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NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

X **Monograph Supplement**

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Reports of Papers

READ AT

The Third Annual Meeting

OF

EASTERN PSYCHIATRIC RESEARCH ASSOCIATION, INC.

Held at

WALDORF ASTORIA HOTEL
NEW YORK, N. Y.

AND

BROOKLYN STATE HOSPITAL
BROOKLYN, N. Y.

In Cooperation With

INSTITUTE OF PSYCHIATRIC TREATMENT
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R. THORNTON WILSON

Mr. R. Thornton Wilson, friend and benefactor of The Eastern Psychiatric Research Association whose generosity made possible the publication of this monograph.

Foreword

THEODORE R. ROBIE, M.D., *President*

It has been stimulating to hold the chair in this third year of the Eastern Psychiatric Research Association's existence. The high standards of our scientific forum set by my predecessors, Dr. David Impastato and Dr. Leo Alexander were recorded in the monograph supplements of *Diseases of the Nervous System* published in July 1957 and July 1958. These monographs delineate various phases of research progress in our times, in the physiological, genetic, chemical and preventive spheres.

The year 1958 will be remembered as the period when the chemotherapeutic treatment of melancholia became firmly established in psychiatric thinking. We are now investigating no less than ten energizers! This third monograph containing the papers presented at our annual meeting at Brooklyn State Hospital on October 23rd and 24th, 1958 (in cooperation with the Institute of Psychiatric Treatment of Boston) and at the Waldorf-Astoria in New York on October 25th, 1958, includes papers on chemotherapy (both tranquilizers and energizers) and electro-, insulin-, and CO_2 therapy.

Our first session covered a resumé of the various forms of psychiatric treatment by Dr. Leo Alexander followed by papers on electroconvulsive therapy, electrostimulative therapy and insulin therapy. The sceond session included appraisals of carbon dioxide therapy, psychotherapy, milieu therapy and drug therapy. Dr. Paul Wilcox was awarded a prize of $100 by the Institute of Psychiatric Treatment for the best contribution during the first day for his paper "The Place of CO_2 Therapy in Broad Spectrum Psychiatric Treatment." At this joint meeting of our Association and the Boston Institute, Dr. Ladislav Meduna was presented the Purdue Frederick Company's Medical Achievement Travel award of $1,500.00.

On the second day Dr. Gideon Eros presented an exceptionally erudite paper on "The Aging Process," and Dr. Leon Roisin a joint presentation with five other doctors on "Liver Pathology Following Tranquilizing Drug Therapy," was flanked by excellent papers by Dr. James Rappa, Dr. Robert Arnot and others.

At the final day's meeting held at the Waldorf-Astoria glimpses of various energizer and tranquilizer therapies, as well as explorations of psychologic, psychodynamic and physiodynamic technics were presented. A symposium on "Building Stones for a Preventive Psychiatry" was a fitting climax to the three-day convention with scintillating papers by Cyril Franks, Marvin Opler, Horsley Gantt and Ralph Gerard. With so many excellent papers, the Prize Award Committee divided the R. Thornton Wilson award among Cyril Franks, Ph.D., Loring Chapman, M.D., John R. Rainer, M.D., Leon Roizin, M.D. (et al.) and Ralph W. Gerard, M.D., whose "Neurochemical Aspects of Preventive Psychiatry," was a most valuable contribution.

As our name implies, the Association is keenly interested in fostering Research in Psychiatry, particularly in the physiological, physiodynamic, chemotherapeutic, genetic, and preventive spheres. Due to the generosity of Mr. R. Thornson Wilson, we have been able to make a good start by presenting awards to those making worthwhile contributions to the literature. We are now ready to foster specific practical research projects initiated in the name of the Association. Psychiatrists wishing to undertake specific research individually or in groups (and particularly our own members), are invited to submit in detail any proposed research project in the spheres indicated, to our Secretary Dr. David Impastato. Our Research Committee will consider the proposal and seek further information when needed from the initiator(s), and award stipends as merit indicates and our funds permit.

It is believed that many of our members may wish to purchase some form of life insurance policy with the Association as beneficiary in order that additional funds may accumulate for these purposes. Some have already done so. Other members may know of philanthropic minded individuals or corporations who may wish to give or bequeath funds to the Association, which as an eleemosynary organization, incorporated in the State of New York, is permitted to accept funds for such purposes. Gifts or bequests of this nature are tax deductible. A form for such gift or bequest is printed on the last page of this monograph.

Psychiatry has arrived at the threshold of astonishing and unbelievable new developments, that can enhance the outlook for mental health in our times. The discovery of the "tranquilizers" only a few years ago, and of the "energizers" only two years ago, have opened new avenues for the enhancement of psychotherapy through chemotherapy. But the fact that we spent over ten billions last year on alcoholic beverages, while only 35 million was spent for research on all types of mental illness, including alcoholism, which is clearly recognized as one type of mental illness, should make us realize that we are only scratching the surface of the major job that should be done by investing adequate funds in this field of research. With your help we can increase materially the research that will be initiated over the coming years.

DISEASES *of the* Nervous System

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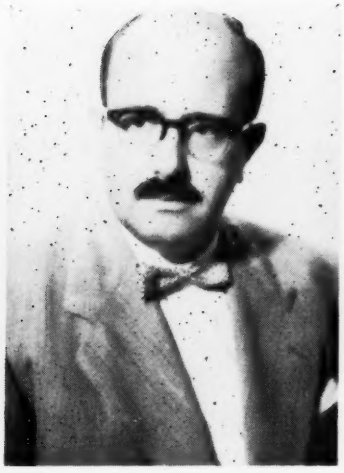

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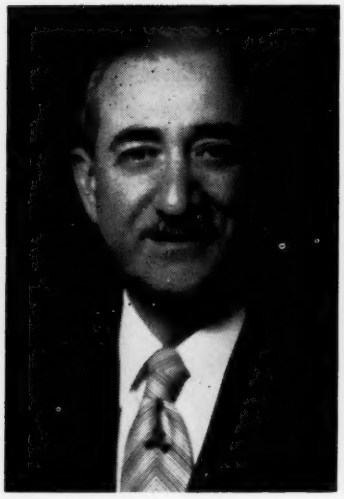

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Dimensional Aspects of Preventive Psychiatry

(Personality Dimensions and the Prediction of Response to Treatment)

CYRIL M. FRANKS, PH.D.

I. Introduction

In an attempt to understand abnormal behavior psychiatrists and psychologists have, by and large, placed reliance upon the predominantly descriptive techniques of classical psychiatry and the explanatory systems of the so-called "dynamic" schools. The outcome seems neither impressive nor reassuring (as Eysenck expertly points out).

As far as description is concerned, contemporary texts are neither internally nor externally consistent. It is consequently not unsurprising that psychiatric diagnoses show little reliability and that many psychiatrists have come to place little reliance upon descriptive and diagnostic categories in their everyday practices. The record is scarcely more impressive when the more fashionable dynamic approaches are considered. Here, too, there is considerable disagreement between the various schools of thought[2] and each of the numerous systems purporting to account for human behavior are internally inconsistent at many levels. It is sometimes fallaciously argued that such matters are of little importance to the busy clinician trying to treat his patients, and that validation by clinical experience is of prime significance. Unfortunately, systematic examinations of over half a century of endeavor fail to support the plea that, despite the theoretical chaos, the patient is improved or cured as a result of psychoanalysis and other forms of psychotherapy. At least two reviews[3,4] of all the available evidence have disclosed the fact that, when the effects of psychotherapy are compared with various estimates of spontaneous remission rates, there is apparently no difference. More recently Hastings, of Minnesota,[5] has reaffirmed the need of psychiatrists to demonstrate improvements which are significantly greater than spontaneous remission rates before arriving at any conclusions about the effectiveness of their therapeutic procedures.

The failure of dynamic psychiatry to achieve very high academic respectability can scarcely be attributed to its recency. Half a century is a long time to ignore the tools and techniques which are available. In general, dynamic psychiatrists tend to appeal to intuition, insight, and clinical experience in generating and evaluating their theories and treatment processes. They tend to reject the generally recognized principles of experimental method[6] and they fail to utilize the numerous techniques of statistical analysis which have been developed expressly for dealing with such problems. Clinical experience and insightful "hunches" are of value in the generation of hypotheses and theories, they are, under no circumstances, acceptable as proof of the validity of these concepts, no matter how plausible they appear.

II. The Dimensions of Personality

It is my contention that only part of the current dilemma is attributable to the above methodological omissions and that, since all behavior is mediated through one or other of the body systems, progress is more likely to be achieved within a genetic or biologically orientated framework. With this in mind I propose to describe a series of researches, some of it as yet unpublished, carried out by my associates and myself over the past decade at the University of London Institute of Psychiatry, attached to the Maudsley Hospital. Implicit in the practice of some modern psychiatrists is the, to me, strange belief that there is a single continuum from normalcy through neuroticism to psychoticism or, as Myerson[7] graphically puts it the, "neuroses span the bridge between . . . normal mental states and certain psychotic states." Sometimes this belief is supported by reference to clinical experience, more frequently recourse is to the authority

From Psychology Service and Research Center, Neuro-Psychiatric Institute, Princeton, N. J.

The author, for this paper, was awarded, jointly with others, the R. Thornton Wilson annual award for his contribution to psychiatric research and treatment.

of tradition. A much smaller group of psychiatrists believe, but with an equal lack of acceptable evidence, that a patient can have both neurotic and psychotic symptoms—after all, a person can have a broken leg and tonsilitis— and implicitly accept a two dimensional hypothesis. In an attempt to resolve this problem a series of statistical studies were carried out in which it was demonstrated that the Freudian or unidimensional theory was incompatible with the evidence, which suggested that two continua or factors, or dimensions are required for the description of neurotic and psychotic disorders.

Such an approach has been extended, under the leadership of H. J. Eysenck, to a statistical examination of the many syndromes and categories frequently subsumed under the heading of neuroticism. The question posed was: is it possible to apply a unidimensional hypothesis to such neurotic classification of symptoms as hysteria, anxiety states, obsessions, etc., and to regard them as differentiated from each other merely in terms of different degrees of severity of illness? There is no time here to describe the complex statistical and testing procedures used, they are reviewed in detail elsewhere.[8] It is sufficient to note that a wide variety of objective performance and questionnaire tests were given to a large number of normal and neurotic patients and the resulting data submitted to various factor analytic procedures. The evidence strongly suggests that the traditional psychiatric syndromes in the field of neurosis, as well as the various psychopathic sub-groupings, can be resolved into two orthogonal or unrelated personality dimensions; namely those of neuroticism and introversion-extraversion.

As is apparent from figure 1 these two personality dimensions are quite independent of each other, a point which had been originally emphasized by Jung[9] but hitherto unverified. Jung was probably the first to point out that hysteria is a syndrome typically found in the extraverted neurotic whereas psychasthenia is a syndrome typically found in the introverted neurotic. Because the term psychathenia is now obsolete Eysenck suggested the term "dysthymia" to describe those introverted neurotic syndromes characterized by anxiety, reactive depression, and/or obsessive compulsive features. Dysthymics, as this cluster will henceforth be termed, tended typically to have high scores on tests of neuroticism and high scores on tests of introversion (with correspondingly low scores on tests of extraversion) whereas hysterics and psychopaths typically tended to have high scores on tests of neuroticism, together with high scores on tests of extraversion (and correspondingly low scores on tests of introversion).

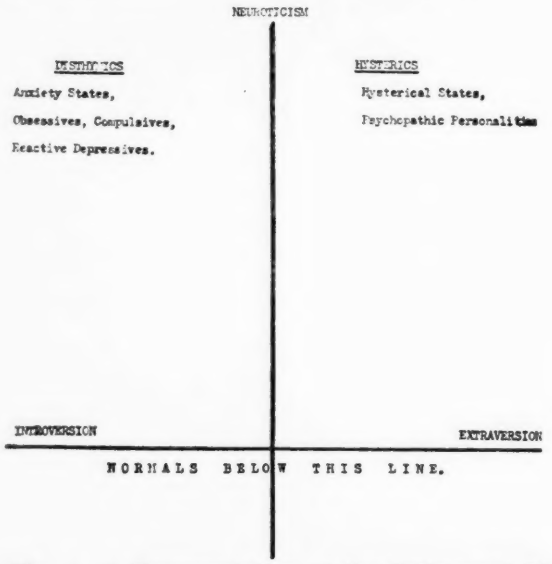

Fig. 1. A Representation of the Orthogonal Dimensions of Neuroticism and Introversion-Extraversion.

Statistically these two dimensions, together with the orthogonal dimensions of psychoticism and intelligence—if one wishes to regard intelligence as an aspect of personality—take up only a small part of the total test battery variance. At this stage two alternatives present themselves. It is possible, like Cattell,[10] to continue the extraction of further factors indefinitely in an attempt to describe as much of personality as possible; it is possible, like Eysenck, to regard this descriptive dimensional extraction of independent personality factors merely as a necessary but static first stage which must eventually be supplemented by a more causal kind of investigation. It is this search for a causal and genetic basis to these dimensions of personality which is of concern here, in particular the dimension of introversion-extraversion, since it is in the understanding

of the underlying constitutional elements of this dimension that most progress has been made. Less attention has so far been given to elucidating the causal factors underlying the dimension of neuroticism, which is regarded as a form of drive possibly related to the overexcitability of the autonomic nervous system, particularly the sympathetic branch.[8] That neuroticism is in part hereditarily determined and therefore constitutionality is strongly suggested by twin studies such as that of Eysenck and Prell,[11] although it must be stated that the conclusion of this latter study have recently been challenged on statistical grounds by Karon and Saunders.[12]

III. The Determinants of Personality

One starting point in establishing a causal basis to the personality dimension of introversion-extraversion is the well-known work of Pavlov.[13-16] Pavlov's theory of cortical functioning emphasizes two basic processes, *excitation* and *inhibition.* It is impossible to define these terms without embarking upon considerable and highly dubious speculation of a neurophysiological nature and it will suffice here to regard them as hypothetical molar constructs, both of which are positive in nature. Inhibition, it should be *noted,* is *not* regarded as merely the absence of excitation. Considerable confusion is brought about, both in the works of Pavlov and other authors, by the unfortunate multiplicity of usages of the term "inhibition," which is widely used in at least three different senses. There is the general psychiatric usage to describe the behavior of the introverted withdrawn individual; there is the more precise, but not clearly understood, neurophysiological use, and there is the Pavlovian usage to describe a hypothetical positive molar cortical process. It should be stressed that central inhibition in the Pavlovian sense, which is fundamentally how the term is used here, should be associated with the *absence* of behavioral inhibition in the psychiatric sense.

Following a plethora of experiments on the conditionability of dogs and the induction of experimental "neuroses" in animals, Pavlov likened the kinds of neuroses developed in his various types of dogs to those found in man. He made many speculations about the causes of various human mental disorders in terms of pathological variations in his two cortical processes, but never followed up any of these observations. One such observation[13] was to the effect that neurasthenics possess an exaggeration of the central excitatory process whereas hysterics possess an exaggeration of the central inhibitory process. Quite different statements have been made by Pavlov elsewhere in his writings and this observation is probably of value chiefly as a starting point for the theory of conditioning and personality which is about to be presented.

By relating Pavlov's statements about neurasthenics and hysterics to his observations upon the conditionability of his dogs it would be possible to predict that neurasthenics would form positive conditioned reflexes readily, and that, once formed, these reflexes should be slow to extinguish, whereas hysterics wouldform positive conditioned responses only with difficulty and that these responses would be extinguished fairly readily. But first we will consider briefly the contrasting terms of neurasthenia and hysteria, or—in terms of our agreed terminology—dysthymia and hysteria. According to Pavlov, implicitly if not explicitly, dysthymics and hysterics differ in terms of some speculative central processes of excitation and inhibition. Centrally the effect may be regarded as a ratio or balance between these two processes, the dysthymic being at the excitation dominated end of the continuum and the hysteric at the inhibition dominated end. Now dysthymics and hysterics have been shown at the Maudsley Hospital to differ not in their degree of neuroticism but in their positions on the continuum or dimension of introversion-extraversion. It seems at least plausible, therefore, to postulate that the causal or underlying physical basis to the behavioral dimension of introversion-extraversion may be conceived of in terms of these two Pavlovian processes of excitation and inhibition.

Support for this argument may be found by an examination of the symptomatology of the dysthymic and the hysteric. Thus, the dysthymic, i.e. introverted neurotic, tends to present the following type of symptoms: anxiety, compulsive thoughts and actions,

over-sensitivity to his environment, hesitance, over-cautiousness. He is often over-aware of himself and too much concerned about his relationships with other people; he may be hyperactive and over-conscientious. All these characteristics can be discussed in terms of Pavlov's concept of central excitation. On the other hand, the hysteric, i.e. extraverted neurotic presents very different symptoms. He tends to be insensitive to his environment and to the feelings of others; he is often impulsive in his actions and his feelings may be shallow and superficial. He tends to be irresponsive and unreliable; he may develop escape mechanisms of a physical nature such as the complete dissociation of a limb or an eye, or of a more psychological nature such as amnesia or a fugue state. Dissociation characteristics such as these would seem to be consistent with Pavlov's concept of central inhibition. Similarly, it is the introverted normal who is often hesitant, conscientious, sensitive and responsive to his environment and who becomes agitated when he has to meet many new people; it is the extraverted normal who is usually impulsive, not so conscientious, less sensitive and less responsive to his environment, and who is usually unperturbed no matter how many strangers he has to encounter.

It will be noticed (figure 1), that the psychopath is classified as an extraverted neurotic. Consequently the causal basis, if the present theory is tenable, should be one on which the psychopath presents behavioral or clinical features which may be essentially associated with the Pavlovian concept of excessive central inhibition.

Before we consider psychopathy in terms of excitation-inhibition and, later on, conditionability, it is necessary to make explicit how this ill-defined and unpopular term is used here. The psychopath, incidentally provides a good example of the confusion caused by the unfortunate choice of terminology. It is probable that the average psychiatrist would describe the irresponsible outgoing psychopath as being uninhibited, whereas I would prefer to regard such clinical behavior as consistent with the presumed state of central inhibition. By psychopathic personality I mean that extraverted nerotic who has had a lifelong history of maladjustment and antisocial or asocial acts, who lacks the ability to control his immediate emotional responses, who is ego-centric, lacking in moral feelings and who adopts an erratic and purposeless way of life. It is typical of such an individual that he is unable to profit from experience or to learn from past mistakes, that he lacks appreciation of shades of meaning, and that he finds difficulty in identifying with the feelings of others. Further evidence for this statement and, in particular, for the characteristic inability of the psychopath to learn from experience will be presented shortly when the relationship between conditionability and personality is discussed.

If it is correct that the psychopath has an exaggeration of this central inhibitory process, then we might expect to find other evidence that psychopathy has a large constitutional element. Nowadays there is general agreement, with certain notable exceptions, such as Lauretta Bender,[17] that certain aspects of psychopathy probably have a significant constitutional basis. Rosanoff et al.,[18] Kallman,[19] and Slater,[20] working with twins, have all provided support for the hypothesis that abnormal character traits are inherited to a large degree. Here we have attributed both psychopathy and hysteria to a predominance of central inhibition and hence we regard both hysteria and psychopathy as in part constitutional in origin. Apart from the evidence already presented there are other findings which are in agreement with this. Thus Kraulis[21] found a high proportion of psychopathic drifters among the relatives of hysterics.

It would seem, then, that the causal or genetic basis underlying the personality dimension of introversion-extraversion might be approached in terms of Pavlov's central processes of excitation and inhibition. The prediction may, therefore, be made that the introvert, be he normal or neurotic, should possess an excess of central excitation and, consequently, should form conditioned responses readily; once generated, these conditioned responses should be extinguished only with difficulty. Similarly the extravert, be he normal or neurotic, should possess an excess of central inhibition and should form

conditioned responses only with difficulty; these conditioned responses should be extinguished readily. Furthermore, contrary to the widely held belief that neurotics as a group condition better than normals, the general predication may be made that conditionability is totally unrelated to neuroticism per se but only to the introverted or extraverted component of the neurotic behavior. In other words, whether a non-brain damaged neurotic conditions well or poorly is independent of his degree of neuroticism and related only to the kind of neurotic he is, i.e. introverted or extraverted.[22]

These crucial experiments were carried out in a sound proof conditioning laboratory especially designed for this purpose.[23] Figure 2 shows a normal subject in the laboratory. The unconditioned stimulus is an air puff delivered to the right eye and the condi-

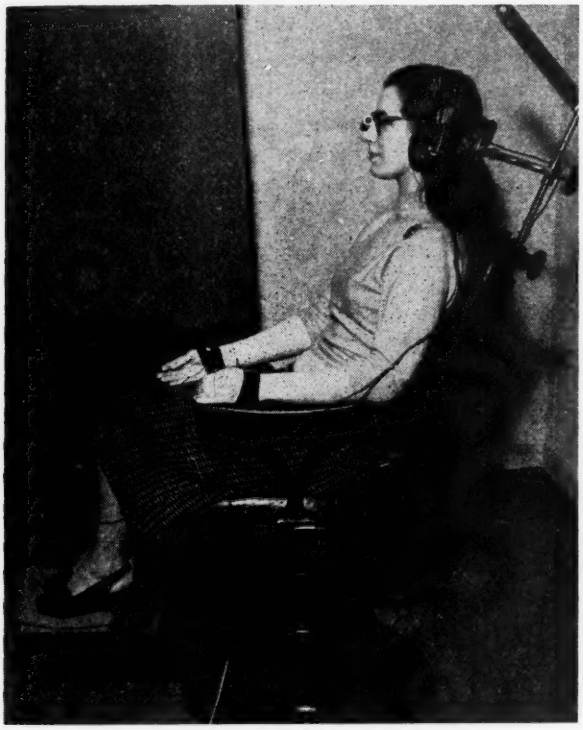

Fig. 2. A Normal Subject Being Conditioned in the Sound Proof Laboratory. (Earphones deliver the conditioned stimulus, a tone; spectacles deliver the unconditioned stimulus, an air puff, and also record photo-electrically all eyeblinks. Electrodes on the hands provide a continuous recording of basal PGR and PGR changes.)

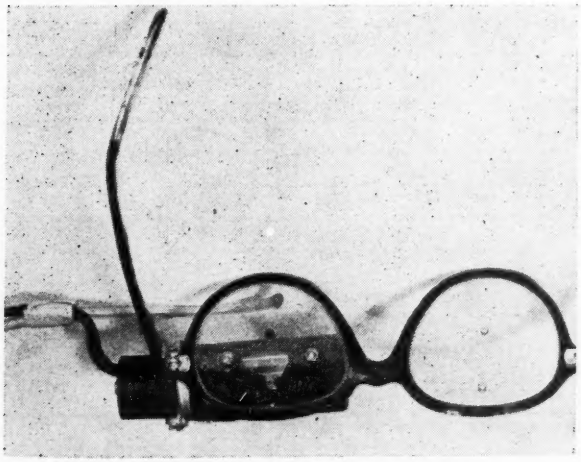

Fig. 3. Photo-electric Method of Recording Eyeblinks. (The same lens which houses the photo-electric cell also carries the polythene tube which delivers the air puff.)

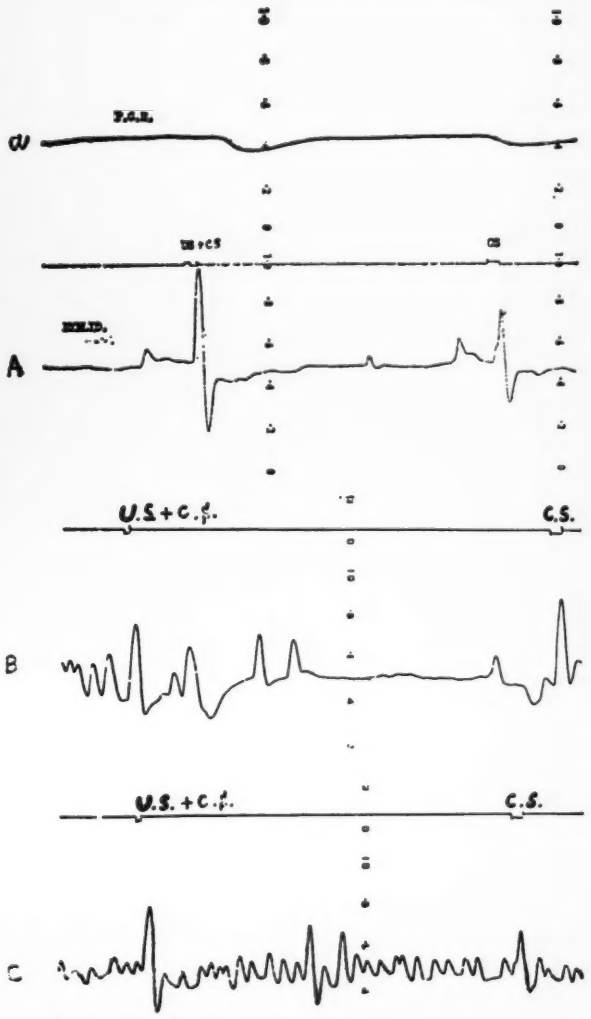

Fig. 4. Some Typical Conditioning Records. (Reading from left to right—"A" represents a conditioned eyeblink response of a subject who gives almost no spontaneous blinking during the variable 20-30 seconds inter-trial interval. Note conditioned PGR changes of this subject ("a"), with the characteristically much longer latency periods. "B" represents the record of a subject who produces a moderate amount of spontaneous inter-trial blinking and "C" is the record of a subject who blinks excessively. In all cases, by measuring the latency, the critical responses are readily detectable.)

tioned stimulus a tone, delivered to both ears via a pair of earphones. The conditioned and unconditioned responses can be either eyeblinks or galvanic skin responses. A partial reenforcement schedule was used, in which 18 acquisition tests trials were irregularly interspersed among 30 reenforced trials. This was followed by 10 successive extinction test trials during which the tone alone was presented. Figure 3 shows the photo-electric method of recording the eyeblinks—a new method which possesses the tremendous advantage that nothing is attached directly to the eye or eyelids.[24] The spectacle frame houses both the photo-electric cell which is sensitive to eyeblinks and the polythene tube which delivers the air puff. Figure 4 presents some typical conditioning records of subjects who vary in spontaneous blinking rate from frequently to very occasionally.

Using both eyeblink and PGR reflexes I found that anxiety states and other dysthymics (all introverted) conditioned significantly better than a group of hysterics and psychopaths (all extraverted).[25] A group of normal subjects, being as a group neither extraverted nor introverted, tended to occupy an intermediate position (figure 5). Furthermore, when the conditioning data were correlated with various personality questionnaires the predicted relationship was found with introversion-extraversion (a high extraversion score being associated with poor conditioning) together with the predicted lack of relationship with neuroticism.

When a similar experiment was carried out with 55 normal subjects essentially similar results[22] were obtained. Figure 6 presents the total number of conditioned eyeblink responses given by the 15 most extraverted subjects (the broken line) and by the 15 most introverted subjects (solid line). Figure 7 presents the total number of conditioned eyeblink responses given by the 15 most neurotic subjects (broken line) and by the 15 least neurotic subjects (solid line). The only study to refute these findings is a student dissertation of Das, who failed to find any correlation between conditioning and either introversion-extraversion or neuroticism. On the other hand, Shagass and Kerenyi,[26] in Canada, recently obtained a highly significant correlation between ease of eye-

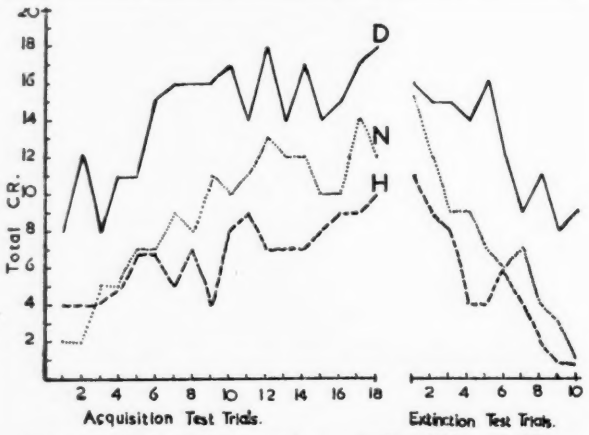

Fig. 5. The total number of Conditioned Eyeblink Responses given by 20 Dysthymics (D), 20 Normals (N), and 20 Hysterics and Psychopaths (H) at each test trial.

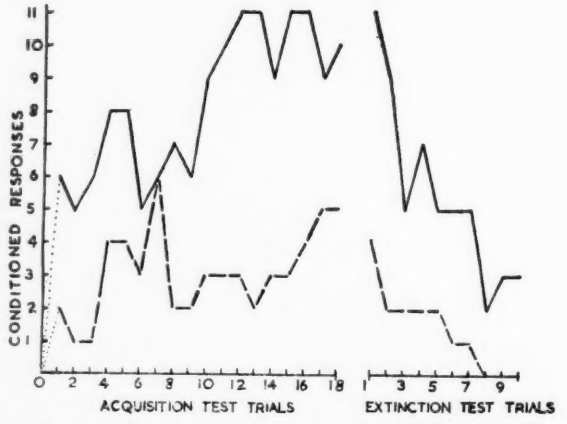

Fig. 6. The total number of Conditioned Eyeblink Responses given at each test trial by the 15 most Extraverted (broken line) of a group of 55 Normal Subjects and by the 15 most Introverted (solid line) of the same group.

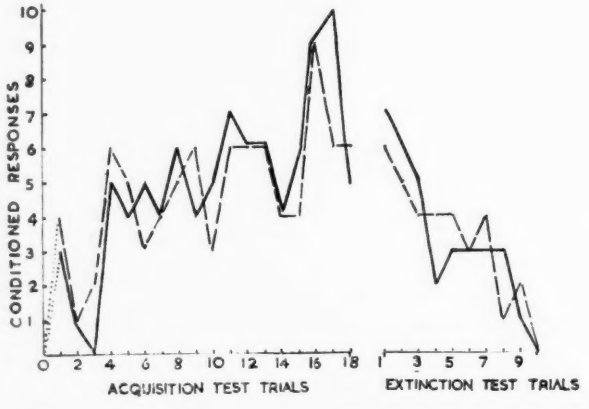

Fig. 7. The total number of Conditioned Eyeblink Responses given at each test trial by the 15 Most and Least Neurotic of the same 55 Normal Subjects used to provide the data illustrated in Fig. 6.

lid conditioning and introversion, using Gilford's questionnaires[27] to measure introversion-extraversion and a conditioning technique similar to my own.

Experiments such as these provide strong support for the theory that the clinical or behavioral personality dimension of introversion-extraversion is related to some physiological quality of the nervous system, possibly excitation-inhibition, which manifests itself in individual differences in conditionability. They also strongly indicate that conditionability is unrelated to neuroticism and make it possible to account for the fact that most previous studies which examined the conditionability of groups of neurotics found them superior to normals, despite the fact that conditionability should be unrelated to neuroticism if the present theory is correct. The explanation is essentially a practical one; among any unselected group of hospitalized neurotic patients the dysthymic variety are likely to preponderate; the psychopaths and hysterics are more likely to be found in prisons or night clubs and to refuse to accept voluntary admission into a psychiatric hospital. For example, in one of the few studies[28] where detailed information about the sample is provided it was reported that no differences were found in conditionability between anxiety states on the one hand and a mixed selection of alcoholics, depressives, obsessives, compulsives and psychopaths, etc., on the other hand. Since both groups contained large numbers of introverted neurotics (dysthymics) it is hardly surprising that no differences in conditionability were obtained!

In another series of experiments[29-33] drugs were used to produce central stimulant or depressant effects. Figure 8 presents the results of a typical study[31] in which normal female subjects were allocated at random into one of three major groups, those receiving dexedrine, those receiving a placebo and those receiving sodium amytal. All three groups differed significantly from each other, the stimulant or excitatory drug increasing conditionability and the depressant drug decreasing conditionability. In earlier studies[29,30] it was found that a depressant drug reduced conditioning as predicted and, at the same time, increased the subject's extraversion scores without alteriug the neuroticism measures.

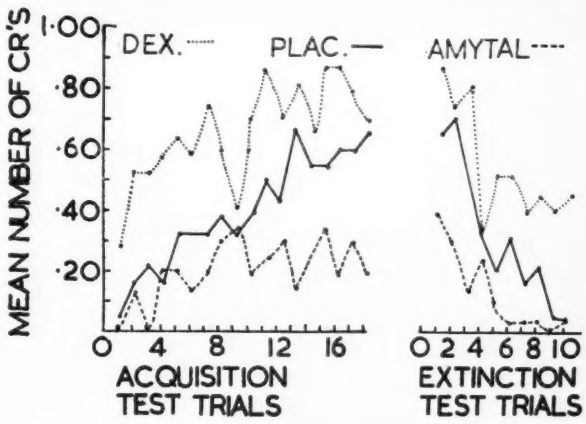

Fig. 8. Mean number of Conditioned Eyeblink Responses given at each test trial by groups of approximately 20 Normal Female Subjects after receiving Dexedrine, Placebo or Sodium Amytal.

The value of some of these findings is limited by a serious difficulty of interpretation. It is reasonable to believe that stimulant and depressant drugs have peripheral actions as well as central ones. For example, Settlage[34] gave cats a dose of amytal whichever was sufficient to prevent the performance of any conditioned response, while leaving the original unconditioned response unimpaired; after recovery from the drug, subsequent testing without any further reenforcement showed that a conditioned response had been successfully formed even though it never appeared during training and testing while the animals were under the influence of the drug. In the drug experiments cited above it is difficult to determine to what extent the findings reflect the peripheral motor consequences of the drugs concerned and to what extent they reflect any direct effects upon a central learning or connection formation process.

Despite this limitation it is instructive to compare these "conditioning curves" of normal subjects under the influence of drugs with the corresponding curves obtained from undrugged subjects belonging to various normal and abnormal extreme groups. The similarity between the conditioned response behavior of normal introverts, neurotic introverts (dysthymics) and subjects who have received a stimulant drug is very evident from the diagrams presented in this

paper. An equally striking parallel exists between the conditioned response behavior of normal extraverts, neurotic extraverts (hysterics and psychopaths) and subjects who have received a depressant drug. The fact that it is possible to simulate certain aspects of neurotic behavior by the application of centrally acting drugs is of considerable theoretical and practical significance.

Central inhibition may be induced artificially and temporarily by a depressant drug, it is also very possible that a similar but more permanent effect is produced by certain forms of naturally or operatively induced brain damage. For example, Gantt and his colleagues,[35,36] as well as myself, have found that certain brain damage subjects tend to form conditioned responses only with difficulty. Thus under certain situations the effects of depressant drugs such as alcohol and amytal, hysteria, psychopathy and brain damage would appear to have some similarity and to resemble the pattern produced in the extreme extravert. The resemblances between hysterics, brain damaged subjects and psychopaths have been well portrayed by Kennedy,[37,38] who postulates a constitutional similarity among all these abnormalities. He points out that diseases such as encephalitis lethargica, which damage certain regions of the brain, can—and often do—result in the occurrence of many psychopathic symptoms. This is consistent with the findings that certain post-leucotomized patients become psychopathic and at the same time more extraverted and poor at forming conditioned reflexes.

IV. Prediction and Prevention

One of the most challenging and widespread problems in modern society is that of the *modus operandi* and detection of the delinquent or potentially delinquent personality. At first impression it might seem feasible to subsume delinquency under the more general heading of psychopathy, but this would imply that all delinquents are extraverted, which is a simplification unwarranted by the facts. However, at least two studies[39,40] have shown that, although both introverts and extraverts can, and do, become delinquents, it is the extraverted child who tends to become the habitual juvenile and adult offender. It may be that certain aspects of behavior which are at present commonly classified together as psychopathic can be further resolved into two broad subgroups, a grop of asocial offenders who just can not conform to society and another group of anti-social offenders who are against society.[41]

This hypothesis is based on the finding that certain psychopaths find much difficulty in forming conditioned responses and that, once formed, these responses are soon extinguished. These psychopaths are also extraverted in personality. It is characteristic of such individuals that they are unable to learn from experience or punishment or to profit from help offered them, whatsoever its nature. Such individuals are those who become the "true" psychopaths, they are asocial in as much as they are unable to learn the rules of society. However, there may be another group of delinquents who are very capable of conditioning and of learning the rules of society. Unfortunately, the rules they acquired from the microcosmic section of the environment in which they exist are regarded as undesirable and anti-social by the vast majority of mankind. From their neighborhood, family, friends and mass media such as the cinema they readily acquire a conditioned pattern of delinquent behavior. If the theory of conditioning outlined here is correct, then such individuals would tend to be relatively introverted.

The concept of recidivism now takes on new attributes and new complexities to add to the existing ones of which we are all too well aware. In the search for the causes which contribute to recidivism many possible factors have been examined. For example, attempts have been made to relate the dimension of intelligence to the incidence and nature of recidivism, but so far no consistent relationships have emerged. When recidivism is examined in terms of the dimension of conditionability, i.e. of introversion-extraversion, two interesting possibilities arise. Some recidivists would have learned anti-social behavior patterns from the undesirable environment in which they live. Even repeated prison sentences, if primarily custodial, would merely provide a reenforcement of the undesirable society whose

patterns they learn so well. These recidivists, if the present theory is correct, could be detected by their tendency towards introversion and by their ease of conditionability in laboratory tests. They are the non-psychopathic recidivists who, if they are highly responsive to undesirable training, should be equally responsive to more desirable treatment in the form of psychotherapy and reeducation, etc. Preventive psychiatry should concentrate on this group of early recidivists and potential lifelong criminals.

At the same time there might exist another group of recidivists, extraverted in personality and very poor at forming conditioned responses. These recidivists should be classified as truly psychopathic, i.e. asocial, rather than anti-social. They would not respond to any form of training or treatment and would probably be constitutionally unable to acquire many of the rules of the society in which they lived. In an era where an acute shortage of psychotherapists and facilities for skilled remedial training predominates, a selection device based on personality and conditioning tests would be invaluable. An interesting, and readily testable corollary is that the introverted delinquents should have come from emotionally or materially undesirable environments whereas the extraverted (more psychopathic) delinquents, being indifferent to social learning, could have come from any sort of environment. Few of the studies which have examined delinquents have related introversion-extraversion to home background in this way.

Although this theory rests on slender evidence and must be regarded as speculative, there is some independent confirmatory evidence which lends support to these conjectures. Lykken,[42] using the PGR as his measure of conditioning, also found that his psychopaths were more difficult to condition than his normal group. His study is extremely provocative in that it raises many interesting possibilities and it is well worth considering here in some detail. Lykken makes explicit a differentiation which has long been implied in clinical practice; he differentiates between the neurotic psychopath (presumably an individual who has high scores on tests of extraversion and on tests of neuroticism), and the sociopath (presumably with high scores on tests of extraversion but only moderate scores on tests of neuroticism). Since both are extraverted, both should condition poorly and this is what Lykken found, despite the fact that he conceived his experiment in an entirely different framework to that propagated here.

Dimensional theory and conditioning as diagnostic and preventive tools could be used in settings other than penological. There is some evidence to suggest[43] that certain postleucotomized patients become more accident prone, as well as more extraverted, sometimes psychopathic and possibly poorer at forming conditioned responses. It is possible that the increased proneness towards accidents in such patients is explicable in terms of loss of those acquired responses which previously enabled them to guard against the many hazards of twentieth-century living. It may be that the accident prone worker in industry could be detected by a battery of tests which include dimensional measures of extraversion and laboratory tests of conditionability.

In a similar manner a combination of personality questionnaires and laboratory tests of conditioning may be of value in the selection of those patients who are most likely to respond successfully to certain forms of therapy, in particular those based upon the principles of learning theory or conditioning. For example, in one study[44] carried out in the Maudsley Hospital, as a result of tests of eyeblink conditionability and introversion-extraversion, the treatment of a phobic patient by conditioning principles was correctly predicted to have a good chance of being successful only if augmented by an appropriate dose of amphetamine to increase the ease of conditioning. In the case of the treatment of alcoholism by conditioned aversion therapy it would seem eminently reasonable to make use of such techniques for the selection of likely candidates.[45]

At this stage it is appropriate to refer briefly to the problem of the existence of a general factor of conditionability. As yet no general factors of learning or of conditioning have been demonstrated and many psychologists doubt the existence of such entities. Although the theory outlined in

the present paper assumes that such a general factor of conditionability exists there is no a priori argument for belief in its reality. There are, of course, considerable experimental data which make this assumption a plausible one. However, strictly speaking, it is impossible to speak of a subject's conditionability until the existence of such an attribute has been confirmed. Nevertheless, from a subject's score on a particular personality dimension and from his ease of forming or extinguishing a particular laboratory conditioned reflex it is still permissible to make use of predictions about his response to a particular conditioned response therapeutic technique provided that the predictions have been validated.

Psychopharmacology is becoming of growing importance, and every day new drugs, particularly stimulants and depressants, make their appearance. Now, if it is correct that stimulant drugs increase the ease with which new responses can be acquired and retained whereas depressants have the opposite effect, then psychotherapy (which may be reasonably regarded as an exercise in learning or conditioning) may profit from the judicious use of the correct drug at the correct state in the proceedings.

In accordance with the theory presented here, one would expect a stimulant drug to increase central excitation and consequently ease of conditioning and, at the same time, make a subject clinically more introverted; similarly, one would expect a depressant drug to increase inhibition, reduce ease of conditioning and at the same time, on the clinical level, make the subject more extraverted. Furthermore, it follows that a subject who already conditions well and is introverted is presumably already in a state of cortical excitation; such a subject would require a very large dose of a depressant drug to sedate him, and only a relatively small dose of a stimulant drug to stimulate him. Conversely, it follows that a subject who already conditions poorly and is extraverted is presumably in a state of cortical inhibition; such a subject would require a very large dose of a stimulant drug to have a stimulant effect whereas only a relatively tiny dose of a depressant drug would be required to sedate him completely.

The confirmatory evidence stems both from clinical experience and from the data of various researches. In this latter respect the many investigations of Shagass and his colleagues are of particular relevance. Unlike Pavlov, who was forced to infer the properties of central processes from observation of peripheral changes, Shagass was fortunate in having the well established techniques of electroencephalography readily available for the more direct observation of central processes. Even before Shagass commenced his studies, there was reason to believe that a relationship exists between certain aspects of personality and the nature and amount of time the alpha rhythm is present in the record, and it now seems likely that such observations are associated with some form of central nervous excitability which is probably of a constitutional nature.[46]

In essence Shagass[47] has apparently demonstrated that the amount of intravenous sodium amytal required to produce sedation, as manifest by slur of speech and plateauing out of the increasing amplitude of fast frequency EEG alpha waves, is least for hysterics and most for anxiety states. These findings are consistent with the supposition that extraverts are already in a state of inhibition dominance and consequently require little additional depressant to sedate them. Conversely, introverts, in a state of excitation dominance, require a considerable amount of amytal for sedation to become effective. Somewhat analogously, Sheldon and Stevens[48] list high resistance to alcohol as one of the criteria for their cerebrotonic temperament. Since cerebrotonics seem similar to dysthymics this is to be expected. Similarly McDougall[49] observed that the extravert is most susceptible to the influence of alcohol, whereas the introvert is much more resistant, the only major effect being tendency to become extraverted.

Present methods of estimating optimal stimulant and depressant drug doses in clinical situations are dependent upon more or less empirical rules based upon criteria such as weight, age, and lethal dosage. The paradoxical and apparently inexplicable results sometimes encounter in the practical application of these criteria may perhaps be at-

tributable to a failure to take into consideration individual differences in excitation-inhibition balance. Weight and age data provide necessary but not sufficient criteria; it may also be essential to have some objective assessment of the subject's excitation-inhibition balance before an accurate predicton can be made about his susceptibility to any specific stimulant or depressant. The experimental findings and theoretical formulation presented in this paper may provide such a way. The dosage required would be predicted from a combined score obtained from the subject's position on the introversion-extraversion personality dimension as measured by a questionnaire and from his position on the underlying central excitation inhibition continuum as measured by procedures such as conditioning. Such techniques would be of value for the avoidance of undesired or excessive drug effects of known pharmacological products and for the investigation of the effects of new agents. It should be stressed that this is, of course, a considerable simplification and that psychopharmacology and conditioning theory present many practical and methodological complications[50] which cannot be discussed here.

V. Conclusion

The theory of conditioning and personality which has been presented here suffers from many temporary weaknesses such as speculation, at present the lack of sufficient confirmatory data, and the possibly premature assumption of the existence of a general factor of conditionability. In these respects it is probably a simplification and certainly incomplete. Therefore, I can do no better than conclude with a quotation from Morris Cohen,[51] "If, per impossible, any theory were as complex as the actual facts, it would have no real value. All theory is a simplification and therefore incomplete."

Author's Note: Although this paper was written while at the Neuro-Psychiatric Institute of New Jersey the researches described were carried out almost entirely at the Maudsley Hospital (University of London Institute of Psychiatry). To my ex-colleagues and, in particular, Prof. H. J. Eysenck, who paved the way, I wish to express recognition and thanks for the many stimulating discussions and invigorating experiences without which this paper could never have been written in its present form.

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Discussion

Dr. Alexander: I would like to ask Dr. Franks, whether he gives inhibitory stimuli. On the chart you show only the excitatory. Did you also alter inhibitory CR, or did you do it without using inhibitory signals?

Dr. Franks: This remains the next stage. I have not used the inhibitory signals.

Dr. Feller: I would like to know the size of your population that you studied.

Dr. Franks: In my experiments I have used groups of 20-25 hysterics or psychopaths or anxiety neurotics and several hundred normals.

Dr. Eliasberg: In the evaluation of your results have you considered the paper of Fechner and Weber?

Dr. Franks: If I may counter in the Potter tradition, how would you apply the Weber-Fechner law?

Dr. Eliasberg: I would apply it in this way: the old logarithmic law points out that response to stimulation, whatever stimulation is given, depends on the present state. There is a lot of interpolation between the present state and the response. Such should all be considered.

Dr. Franks: But ours is a study of groups. It applies to groups of individuals in varying states. Therefore this will cancel out for large groups surely.

Mrs. Lipsett: I noticed you gave an extinction trial. I wonder if you could tell us if there was any correlation between the conditioning and extinction.

Dr. Franks: This varies with the response you are

trying to measure. I can send you some data. This is essential, the problem of correlation between one measure and another if this theory is correct. You cannot speak glibly of a person's conditionability. We are too apt to do this. This is only true if we assume a general factor of conditionability. There is no a priori reason why there should be a general factor of conditionability. If that exists, is our theory correct? To answer this one would have to condition a group of people on many reflexes, many measures of their acquisition, extinction and all sorts of modalities, factor analyze them and then show the general factor that ran through them and only then speak of a person's conditionability. Then you could tell how they were conditioned on a particular response. Your question is what is the correlation between extinction and acquisition, if indeed there is some correlation? It is significant.

Dr. Luwisch: I wonder about the selection of anxiety on the one side where there is introversion and hysteria on the other side. We know very well that many hysterias are anxiety hysterias. How would you split them as you did no your chart? Also I would like to ask you whether you separate the true psychopathics from the so-called sham psychopathics, whether you investigate their background. On the one hand is their early mothering responsible for their being true psychopathics and those who are not true psychopathics have they had a fairly normal mother.

Dr. Franks: I did not put in, for simplification, a group of mixed neurotics. There were quite a number of people mixed. This is where the anxiety hysterias came in. Briefly, the question of the sham psychopathic is an extremely interesting one which we want to investigate. I think you are alluding to Boulby on maternal influence. May I refer to an article by Neil O'Connor in Acta Psychologica last year. He wrote an extensive article, not quoted too much, which devastatingly criticizes the work of Boulby, which consciously or unconsciously distorted the works of Goldfarb and others, which was rather premature, as Boulby himself admits now, and his assumptions and conclusions at least must be regarded with care and caution. But we are interested in the sham as compared to the true psychopath and we can make various predictions about this. For example, if the true psychopath is independent of his environment, if it is something constitutional, he could come from any environment. The early years with good, bad or emotional, physical environment would not matter. He would still for constitutional reasons be a psychopath. On the other hand, the pseudo psychopath or if you like the person who is antisocial, not asocial, presumably, if he is in our model, more introverted, conditions well. He could only have come from either a physically or mentally undesirable, environment because he must have learned the wrong things.

This is the next phase in the proceedings, to look at these so-called psychopathic behaviors and analyze and see if we can break them down in this way. This yields clearly a test for prediction. At least we will know if it will be confirmed or not.

The Contribution of Social Psychiatry to Preventive Psychiatry

MARVIN K. OPLER

If Alfred North Whitehead was correct in calling all nature a structure of evolving processes, then psychiatry may well be described as a study of the etiology and dynamics of mental disorders seen in their total environmental setting. If the human world is to be included in a philosophy of science, such evolving processes *are* the reality. Biosocial relationships become the topic for research. Psychiatry is encouraged to proceed on the broad front of dimensional psychology, conditioning experiment, biochemical and genetics research. But the suggestion is clear that these are parts of people and parts of processes; and the behavioral sciences must seek to understand these segments in a *total* process and so interpret them.

In an earlier volume called *Culture, Psychiatry and Human Values,* I stated that mental illnesses could also be viewed as processes which had changed markedly in human history.[4] The social and cultural settings of illness had changed. The developmental course and epidemiology of various disorders had changed. Techniques of prevention and modes of therapy were also in the process of change. Viewing the history of psychiatry, and its present expansion in social psychiatry, we were forced to conclude that new methods, theories and directions must emerge in this medical discipline.

Modern studies in psychiatry, dealing with complex variables such as typology of illness, diagnosis, treatment and outcome, no longer can exclude through arbitrary and shortsighted research design an equal emphasis on the types of persons, patients or therapists, well or ill, who operate in any social and cultural milieu. For this reason, social psychiatry lays claim to being a more thorough, inclusive and searching psychiatry. That it may produce greater coherence in any sub-field of the larger discipline is illustrated by various Scandinavian ecological studies of genetics in which *probands* of relatives and whole communities are searched and evaluated by psychiatrists, in a manner reminiscent of Franz Kallmann's work in this country, or in our Yorkville or New York City studies of epidemiology in which culture-personality theory in anthropology was part of a study of personality development, or of mental health or illness, in communities studied by a combination of scientific methods useful to psychiatry. I have now reported four complex stages in the methodology of the Yorkville-New York Studies, called *Epidemiological Studies of Mental Illness: (Methods and Scope of the Midtown Study in New York).* And this is published in the *Symposium on Preventive and Social Psychiatry,* issued by the Walter Reed Army Institute of Research, in Washington, D.C. The total *Symposium* by an international group of scholars representing various countries illustrates that when we deal with broader questions of illness or therapy, we join hands in concluding that no fact about human conduct, normal or disturbed, in one society or another, or in special settings of industry, in hospital, or in warfare, can utimately achieve a final significance without reference to individual culture, value and social meaning. Consequently, the psychological field in which human behavior takes place is always socially and culturally constituted since man's responses can never be wholly reduced to stimuli derived from an entirely "objective" physical world.[5] When modern psychiatry faces our own contemporary cultures as it must, it requires knowledge of social psychiatry and medical history concerning the changing styles and current variability of behavioral disorder. While the clinician's investigation of individual personality balances can be helpful, the broadly oriented exploration of varying human needs and values in changing social and cultural settings becomes indispensable.

From Department of Psychiatry, University of Buffalo School of Medicine.

Why are these larger parameters, influencing not only the individual case, but the larger groupings of cases as well, so very crucial in psychiatry? For the past six years, from 1952-1958, our studies with Dr. T. A. C. Rennie in Yorkville have been interested in the social and cultural backgrounds of mental illness in the east midtown section of the city. We do not find mental illness randomly distributed in the adult population, ages twenty to fifty-nine. We were concerned with the epidemiology of such disorders throughout an entire population in the neighborhood of 170,000 persons, not just those in treatment, but the treated and untreated both considered together. Various aspects of the study are of interest here. At least half of such a population shows evidence of psychiatric disabilities of a type which could well benefit by treatment. We have already reported that approximately 75% in the sample as a whole were found to manifest significant symptoms of anxiety. About one-third of this population were foreign-born immigrants and two-thirds were in the first to third generations of a half-dozen dominant ethnic groups each tending to live in a specific neighborhood of the community. To a large extent, lower and lower middle class status corresponded heavily to this membership in ethnic communities. Cases of severe disturbance, for example, were found to be 28% in such lower class ethnic segments to 18% in the middle class and only 9% in the upper class. In community studies we had hypothesized that per capita such rapidly acculturating communities as the Puerto Rican, or communities rapidly diminishing in size like the Hungarian would show evidence of greater psychiatric disabilities both in extent and seriousness, and this likewise proved to be the case. In short, the social class and ethnic groups most in need of treatment, that is evidencing the most psychiatric disorder both in extent and seriousness, were the groups by and large receiving least treatment. Social and cultural backgrounds not only were germane to the illness process, but at the same time determined who were in treatment and where brakes were applied to this illness process. Obviously, both cultural and social class status played a role conjointly in producing stresses leading to illness and in insulation of individuals from treatment.[9] In a Canadian study of about the same time, representing rural and small town components, 37% of the population were adjudged by psychiatrists to be "psychiatric cases" requiring treatment, whether or not they received it. Obviously, such epidemiological needs in city or town are not met with the current organization of psychiatry.[3]

If one wishes to focus particularly on social factors influencing treatment of mental illness alone, the New Haven study of Hollingshead and Redlich is instructive. We cannot repeat too often, say these authors in their summary chapter on implications, that "this study dealt only with patients under the care of psychiatrists" (p. 358). In reading *Social Class and Mental Illness,* hasty readers and reviewers have already overlooked this caveat in favor of such absurd conclusions as: (1) lower classes have nine times the amount of schizophrenia as upper classes, which are more prone to psychoneurosis; or (2) even more carelessly and stereotyping, schizophrenias are lower class diseases. Of course, unlike the Yorkville Study or the Scandinavian studies to which we alluded earlier, this New Haven Study is not one of incidence of disorders throughout a population, or as the authors say, not one of "true prevalence" in the least. Its role is to investigate the performance of psychiatry, private and institutional, as it functions to act as a brake on mental illness that comes to treatment. Again we learn that such brakes are ineffectively applied, far too little and much too late, in the mental illnesses of lower classes and New Haven ethnic groups. In the pile-up or prevalence of treated mental illness, in the types of diagnoses applied, and in the kinds of psychiatric treatment people receive, this class and ethnic structure is determinative. Similarly to Yorkville, 66% of the community are Italians, Irish or Slavic-speaking (though Yorkville adds German and Hungarian or Puerto Rican to this percentage). Exactly like Yorkville, British-Americans are 12% and tend to fall into higher class categories while other groups fall into the lower side of the socioeconomic watershed. The nine to one class ratio in schizophrenias, threat-

ening lower class and cultural groups, is part of the same picture of such patients having discontinued first temporary treatments early and abortively. Lack of cultural training and class perspective in the profession may be as germane as class distance in promoting insulation from treatment. As the book indicates, there is certainly cultural variability in both illnesses and attitudes and in a range running from child-rearing practices on out.[8]

In our own work on cultural variations in schizophrenias, as reported in *Scientific American,* the *International Journal of Social Psychiatry* and elsewhere, we have been less concerned with the treatment variables of Hollingshead and Redlich than with the profiles of etiology and dynamics crucial in therapy or prevention. Just as anthropology has documented a tremendous variation in cultures and sub-cultures, so social psychiatry must trace such illness profiles if it is to provide practitioners with viable tools for reducing cultural and class distance.[6,7] The New Haven figures of those in treatment —29% foreign-born and 35% children of immigrants compare with our New York data of one-third foreign-born and a total of 66% in Irish, Italian, German, Puerto Rican and Slavic-speaking groups in the general community. In discussing for New Haven the "paths to the psychiatrist," Redlich and Hollingshead reminded one of what is heard in New York or elsewhere of those on "waiting lists" of clinics and their heroic efforts to get treatment, or of those who had no conception of treatment at all. The authors noted for this "tranquilizing era" of wonder drugs that lower class schizophrenic patients may be discharged from treatment, but that although half experienced this once, "if he is returned to the hospital, the chances are very high that he will remain there indefinitely." In our national figures, where temporary discharge rates for remission have gone up appreciably, it is striking that they exactly equal rates of readmission of which Hollingshead and Redlich write so balefully. Their data and ours lead away from the conclusion that all is well in the Tranquilizing Era, any more than it was in the pre-existing Aspirin Age, since they find the new drugs are not permanently emptying hospitals or lessening "differences in duration of treatment" that exist for psychotics along class lines.[8]

Perhaps the most striking finding in the New Haven study is that least publicized. Beyond the obvious difficulties of ethnic and lower class membership, we learn, page 235 (Table 16), that the incidence of the neuroses is not linked with class, while those figures for re-entry into treatment and prevalence or pile-up of illness are significantly connected with class and ethnic status. At the same time, and expectedly, the incidence of psychoses in the lower class rises to three times that of the upper classes.[8] My former colleague, T. A. C. Rennie, did work on prognosis in the neurotic illnesses which is very relevant here for he established that prognoses in an appreciable number of psychoneurotic cases in the Henry Phipps Psychiatric Clinic could have malignant or psychotic outcome. That we are not dealing with the "unit psychosis" but with a continuum running from "well" to "ill" and to "severely ill" seems patent in Rennie's work, in our Yorkville Studies, and in the reported work from New Haven.

A wide variety of studies in social psychiatry deal with such prognostic indicators, with rehabilitation processes, or with the treatment determinants of Hollingshead and Redlich. In England, where the term, social psychiatry, is most congenial, it has long since led to such innovations as open hospitals, experimentation with day or night institutions, group psychotherapy, milieu therapy, and parallels of Querido's home treatment services in Amsterdam. Much of this has the ring of action programs bringing organizational improvements in their wake. Like Hollingshead and Redlich's work, it has to do with treatment determinants. Recently, in reviewing the Greenblatt-Levinson-Williams' *The Patient and the Mental Hospital,* I was reminded that American work reflects a similar sociological interest in the social structure of the hospital and its psychological impact.[2] The appearance of Caudill's *The Psychiatric Hospital as a Small Society* did not disabuse me of this belief, and in fact sharpened the trend away from the baseline study of this type, the Stanton and Schwartz *The Mental Hospital* which, it had seemed to

me, was more intrinsically dedicated to etiological and dynamic questions than to purely administrative ones alone; or at least concerned with items in such profiles, like withdrawal and resentments from the patient's point of view. In Levinson's concluding chapter and in his co-authored papers, at any rate, there is some retrospective interest in previous backgrounds of patients and their implications for therapy. The section edited by Greenblatt is also interested in *roads from* the hospital and hence in community relationships.[2] In the whole movement from custodial to therapeutic care, one must note besides the typical routes and social structures *inside hospitals,* affecting therapy, and *from hospitals,* affecting rehabilitation, a whole series of roads and systems of stress by which people are swept into illness and hospitals alike. These basic systems in family, culture and community are of the most special importance to preventive psychiatry. For this reason, my own studies in New York or cross-culturally elsewhere have been on social and cultural backgrounds affecting epidemiology in communities, or else effectively determining the etiology and dynamics of specific forms of mental illnesses such as the schizophrenias. When Caudill describes the shattered expectancies of Mr. Esposito in the small society of the New Haven hospital,[1] and these expectancies are in part cultural and not dissimilar to our own findings for male Italian schizophrenics in a sample,[6] then the intervening links of background to therapeutic failures of the Hollingshead-Redlich studies are being provided. There are more Mr. Espositos than the one single case described in some depth in this book. Would that they were described also! For this is more the kind of material urgently required in preventive and community psychiatry. The same variables that enter into success or failure in the hospital enter into recovery and rehabilitation and into the etiology and prevention of illness in earlier stages.

A social and cultural psychiatry is by definition closer to community psychiatry, home treatment programs and better integration of psychiatric services with the social and cultural milieu. In this sense, the focus shifts more to study of both patients and troubled persons in the community, with emphasis upon their cultural background, typical family structures and the differentiated structuring of their illnesses. The ultimate in social psychiatry is both greater knowledge and application of that knowledge of etiology and dynamics of types of illness in their total social and cultural context. The fact that on both sides of the Atlantic such research and treatment perspectives are now broadening to assessments of social and cultural identities, meanings and ways of life prior to hospitalization is a matter for optimism in all fields of psychiatry. It opens the way, at last, for study of neurophysiological correlates, biochemical effects, or personality dimensions within stricter samples of given behavioral disorders and psychiatric illnesses, whereas previous studies of those who come into therapy have been forced to use a non-dynamic and rigid or often outmoded nomenclature. We feel the patient and his culture may be considered more realistically once we cease to make theoretically useless and abstract dichotomies between patients and troubled people of a community, between hospitalized and ambulatory, between social and cultural stresses inside hospitals and outside, and between therapeutic needs before and after hospitalization. Besides viewing the patient and the institution as having social and cultural characteristics, we might additionally view the illness structures themselves as having these characteristics. This is what we mean by including illnesses in Whitehead's definition of nature as being a structure of evolving processes seen in their total setting. For, as Einstein noted, "The formulation of a problem is often more essential than its solution." While psychiatry has been solving problems, even the most cursory view of epidemiology and current statistics suggests that it may not have been solving the right problems first, and the ancillary problems of neurophysiology, biochemistry and dimensional psychology on the basis of such primary solutions and samples. At any rate, both preventive psychiatry and community planning of resources stand to benefit by research on these major social variables of modern cultures.

In the Yorkville Studies, such groups were

surveyed for the epidemiology and typology of mental disorders, with special emphasis upon such aspects as typical family organization, the patterns of handling social and cultural stress, and the development of kinds of problems within these family situations which might be called socially pathogenic. However, while these Yorkville Studies laid stress on epidemiological considerations initially, in later stages they emphasized the dynamic, longitudinal, depth studies of pathogenic families and specific disorders. Probably our most fruitful direction began when global epidemiology became a baseline for moving in a more clinical direction, analyzing hospital samples from our known communities on the basis of normative community predictions. At this point, knowing the continuum from "well" to "ill" and its particular problems, we were able to hypothesize, predict, distinguish and differentiate cultural variables in schizophrenias and other illness forms. We had, then, something of clinical as well as programmatic importance which psychiatrists not only of organizational interests, but privately in practice could apply. It was proposed to deepen knowledge of social and cultural variables appearing in supposed "entities" like the schizophrenias. But as often happens where such variables are strongly patterned in life experience, where neuroses are social and endemic, or where—in L. K. Frank's phrase —"society is seen as patient," the continua of "well" to "ill" became a series of structures of evolving processes, or illnesses culturally differentiated and distinct.

Currently, there is great dissatisfaction in the field of psychiatry with the older diagnostic estimates of Kraepelinian extraction, in contrast to such more clearly defined, organically invariable entities as toxic psychoses, Korsakoff's syndrome, etc. The dissatisfaction stems from a lack of similar precision in the use of schizophrenias, depressive states, alcoholism or psychoneuroses as labels. Yet we know clinically that despite the scarcity of information such labels yield regarding causation and possible patterns of psychodynamics, they refer to a wider range of possibly more serious problems of importance locally and throughout the world. Still less do the diagnostic labels indicate preferred therapeutic approaches or even prognosis. Studies of therapeutic relationships by a wide range of authors like Levinson,[2] Hollingshead and Redlich,[8] or Fink, Kahn, Pollack and Jaffe,[10] all indicate that the labels often measure the social and cultural distance between physician and classes of patients more than they indicate an invariable disease pattern. Anyone who has assiduously attended clinical conferences knows that they have been used as generic labels at best, and at worst that the assumption is made that they define a "kind" of mental disorder. It is questionable, or at least assumptive to a social psychiatrist who knows something of cross-cultural variability to state that there are unit psychoses or fixed and invariable illness entities. The method of applying such nomenclature has been to attach the terms as defined in some historical epoch of Western or European classification to a broad grouping or catalog of symptoms within the category. One then classifies the patients within the illness grouping if they appear to have some undefined number of the symptoms. Such method is classificatory and descriptive in only the roughest manner, and moreover, unlike modern medicine, it does not describe either etiology or dynamics.

Approaches to problems of schizophrenias, depressive states, alcoholism or psychoneuroses often have been marked by numerous confusions and a sense of the *mystique* if not mysticism. Recently, before Fromm-Reichmann and others, one could add a sense of therapeutic nihilism for psychotic states in general. The game of playing with labels in this fashion seems circular in both logic and methodology. One begins with symtoms which even in 1896 were not intended to be either etiological or truly psychodynamic, and ends only with the same broad and nondynamic classification with which one began. We are not inveighing against a beginning in a science through classification and the marshaling of descriptive data. Most sciences begin this way, and move ahead to the delineation of dynamic processes necessitating a series of reclassifications. But behavioral sciences have moved far since 1896 and may join hands in developing dynamic and etiological postulates. A number of

studies have been launched to throw light on the ways in which psychiatrists and psychoanalysts arrive at diagnoses.

While one may disagree profoundly with the Existentialist anthropology and phenomenology sweeping the Continent, these positions have challenged Kraepelinian psychiatry basically, as did Freud with whom the Existentialists ironically disagree, by insisting that *meanings* or symbolic constructs, important to the individual in subject-object relationships, grow out of individual experience and are the indispensable matters to study and understand. A number of passionately held post-Kraepelinian positions —Freudian, Neo-Freudian, Existentialist, or Sullivan's interpersonal communication theory—all stress subjectively felt experience, some coming closer to value orientations or environmental structuring like the Existentialist, and others to subjective symbols, family relationships and energy utilization like the Freudian. Because such systems are intended to be generalizing and pan-human, the basic social and cultural backgrounds are not differentiated. But obviously values orientations, environmental structuring, subjective symbols, family relationships and the content of all human relationships or repressions and suppressions are socially and culturally structured. Accepting the importance of meanings and human communications in such systems, we are adding to their insights that any approach to such categories as mental illnesses in the forms not too familiarly known as schizophrenias, depressive states, alcoholism or psychoneuroses must view these illnesses as *structures* in the plural. That is to say, each one, like the schizophrenias, may require further functional definitions according to social and cultural variables before we can begin to describe etiology and dynamics as a structure of evolving processes. Such terms for illness are far from statistical cross-sections of humanity that are unchanging from decade to decade. They should be viewed in the plural as illness structures requiring immediate, further definition according to social and cultural variables. Once such personality dimensions and profiles are ascertained, the search for neurophysiological correlates and biochemical controls or effects of these more standardized psychic states will become possible. Until then we are studying statistical conglomerates in an outmoded nomenclature which cannot accurately describe existing illness structures or processes.

Put more simply, in an epidemiological study such as Yorkville's, much time and effort went into complex processes of sampling to determine new categories or classifications of both treated and untreated illnesses. If one proceeds as a social psychiatrist with such individuals in their family, social and cultural setting, prior classifications seemed strained and unconvincing. Whatever the generic similarities, no two cases are exactly the same, and this very subtlety of each case is exactly what the classical nomenclature has missed. Such existentialist categories as *individual* subject-object patternings of experience are equally disappointing, however, since they produce their own reductionism to the individual case. Yet in these same samples, particularly if one works to control variables by research design, one notes the cases fall into *deterministically generic patterns in terms of social and cultural variables.*

Social psychiatry therefore places the *locus* of disorder not simply in the individual, but at the same time in the family, society and culture. Mental health or illness becomes a special part or aspect of specific sociocultural systems. Inquiries into *how much* gross disturbance exists, in class and cultural groups, will explore current therapy-needs while investigations of the etiology of illness in individuals, families, and communities are intended to provide social psychiatry with techniques of prevention and leads to more organically founded research.

It is in this way that the Freudian model of an energy-distributing mechanism, uniform for the human species, has undergone modification. Freud's patients came mostly from a single Western European and middle class cultural background. He observed the similarities and was able to generalize about dynamic factors common in such individuals. Because of the uniform cultural factors which were a part of the ego-structure of his patients, he was less able to notice this dependence on a similar sociocultural set-

ting. He, therefore, regarded their personal needs and typical conflicts as coming from a uniform instinctual source which he took to be universal. Today it is realized that it is necessary to study the development and breakdown of personality structure in a variety of cultures and sub-cultures.

In a Neo-Freudian system, it is recognized that both the psychodynamics and psychopathology may vary. By the psychodynamics we mean fluid and personally meaningful forms which agree with minimal conflict in a larger total psychopathology or adjustment state. The psychopathology is the integrated structure of a mental disease process including its historical occurrence and its transformations. Psychodynamics points to balances and imbalances in the individual, but this includes forces in the social environment contribution to personal dilemmas. While medicine and psychiatry have tended to deal with ever smaller units of specialization, social psychiatry expands the horizon to a whole view of personality and group psychological phenomena in response to total environment.

How then does this differ from notions of homeostasis? A whole school of human biologists and cultural anthropologists have tended to agree with Von Bertalanffy that the world of symbols and cultural values may be in conflict with biological trends that then become displaced, possibly generating forces that cause behavioral disorders. Homeostasis implies an organism maintaining some sort of equilibrium in an environment. The thermostatic feed-back model of such a mechanism is viewed as having circular, internal processes, allowing for self-regulating and purposeful behavior in the service of organismic constancy and maintenance. Yet in biology, as Von Bertalanffy notes, there is another set of processes related to "a dynamic interplay" of forces within the living system but without "fixed homeostatic mechanisms." The whole field of growth, reproduction and decay runs counter to "organismic constancy." In psychiatry also, the basic normative models must deal with such cycles as development, maturation and deterioration; and the feed-back system is without strict past, present and future demarcations as in a classical Freudian psychogenic system. Further, the "outer culturally integrated systems" are constantly registered within and affect the individual. Such systems have no mechanical boundaries separating them from the individual for whom there are no snug containments or insulations from environment. Forms of schizophrenia may approach such "encapsulation," but as we have learned in social psychiatry, even such individuals are only all too deeply responsive to environment as if the normal sensitive reacting outer layers were eroded away by painful experiences.

The theoretical model we have constructed is substantiated, as we have said, by known differences in the rates and prevalence of various types of disorder in different environmental settings. The task of a relational science of personality, as in any science, is to account for such variations with as few general constructs and laws as possible, but without destroying the conception of essential relationships. Thus, individualistic theories, or purely motivational psychogenetic theories, ignore the spheres of cognition, ideology and values useful to the anthropologist in discussing the environment, and substitute motivation. Sciences of total personality and group adjustment cannot substitute the *why* of behavior (motivation) for the *what* or content of mental functioning. Both are important. In addition, we need to know *how* people adapt in socially and culturally differentiated situations. The variations in human symbolic processes, in *meanings* from one to another group, suggest that the line between personality and environment is an abstraction. Protective habits, defences, symptoms and even diagnoses vary, requiring specific knowledge of total personality settings. These open systems involve physiology, personality, families and peer groups and wider social settings such as subcultures and classes. In preventive and social psychiatry, consequently, all such relevant scientific specialisms must be mobilized to operate together. In modern societies undergoing rapid social change, it is important to realize that such primary groups as families, peers and neighborhoods, while they have significant roles in maintaining the potentialities for growth, maturation and mental health are the very units

in society often least able to function most effectively in promoting useful balances, adequate social controls or healthy ethical norms. A society in which these groups show pathology is one which requires local analysis and mobilization of scientific resources to prevent further disintegration.

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Discussion

Dr. Meduna:

I have no question to ask but I would like to make some remarks. One pertains to the role of the psychiatrist himself in the diagnosis of the disease. If one did studies in psychiatric case histories and diagnoses of the 16th, 17, 18th and up to the middle of the 19th centuries, it will be found almost impossible to identify any medical disease that was described in those reports in modern terms. They are just not recognizable. The first man, for instance, to describe the use of convulsive treatment in psychiatry was Oran Berger in the early 18th century in Vienna. He used camphor in a disease that is described as "malnor," which is characterized by confusion, but the diagnostic problem was a diminishing of the testicles. I never saw anything like that in my life.

As recently as when the CO_2 Association made the study about the usefulness of CO_2 treatments, the IBM machine showed the diagnosis is absolutely irrelevant to the result the physician achieves. The factors which were relevant were the symptoms. That means there are diagnostic categories which are simply based on the education or scientific bias of the doctor who is apparently just a part of the whole picture as the patient himself is, which I think gives a very deep understanding of the problem we are facing.

I have just one worry about it: If we have to expand our evaluation to the limits the speaker expected from us, very few of us would be able, probably not myself either, to encompass the whole field. It brings up our need for a precision method in humans, approachable by some analyzable machine or apparatus that will yield the data on which to base some sort of a new classification or some possible prediction to some mode of procedure.

Dr. Opler:

I want to indicate my complete agreement with this kind of perspective. I would say this Eastern Psychiatric Research Association itself was an indication that research is needed to help answer some of the questions that are most crucial. I assume that psychiatry will have to face up to this on an international, worldwide basis in terms of illness, etiology, and the indications we are getting on it from epidemiology, not only transformed in our own Western culture and history but in other parts of the world. Also we would like to extend help and psychiatric training not existing elsewhere.

Dr. William Malamud:

I would like to express my admiration for Dr. Opler's point of view and state this, that perhaps it gives us an indication of how terribly important it is at this time in psychiatry to engage in transcultural studies. No matter how adequate our studies are in the individual, whether physiological or psychological, no matter how fundamental our findings may be, we will never understand the process, whether it be schizophrenia or neurosis, unless we transcend cultural boundaries and try to see what the superimpositions of the various cultures are. That may be even more important than the actual fundamental factors that we find in studying the individual.

Application of the Conditional Reflex Method to Preventive Psychiatry

W. Horsley Gantt, M.D.

Prophylaxis in medicine has eliminated the great scourges of the middle ages which decimated the human race—bubonic plague, cholera, small-pox, and more recently, typhus, tuberculosis. No such advance has been made in psychiatry. Indeed this subject is only beginning to emerge as a science. In order to prevent, knowledge as to the cause is necessary. Detection before the disease actually occurs is essential.

Several approaches to the problem have been developed. Among the most fruitful is the study of genetics (Kallman et al.). This leads to a high degree of predictability of the susceptible and it could be a most potent weapon against psychiatric disease. Its usefulness is at present limited owing to the difficulty of social regulation. In a more rational society genetics would gain in importance. At present its findings could help in indicating which individuals are likely to become psychotic under stress.

The method which I outline would include information derived from genetical studies (heredity) combined with a rational basis for classification into types (biochemical, functional). This would involve a study of the specific individual to determine his susceptibility leading to the prevention of psychosis. Prevention would make use of the appropriate drug suited to the personality ("constitution") of the individual.

Neuro-physiological and neuro-chemical bases undoubtedly exist for normal as well as pathological behavior, but the conditional reflex (CR) functional test has shown itself in my laboratory to be a far more delicate barometer than any other presently known method. Thus a deviation from the norm established in an individual, as measured by the excitatory and inhibitory CR's will show impairment of function long before biochemical or neurological tests,[1] eg., a dog deprived of pyridoxin for as little as four days begins to show disturbances in the balance between the excitatory and inhibitory CR's, while blood counts and other bio-chemical examinations reveal no abnormality until weeks or months of pyridoxin deficiency. The CR test will also detect the effect of anoxia (altitude) long before any other test applied and it shows that impairment on this higher CR level may persist a year after other signs have disappeared.[2,3]

At the present I have elaborated a method of detecting which individual dogs will develop nervous disturbances long before there is any other evidence. This is done by 1) the establishment of the normal CR's (+ and —) in that individual, 2) the imposition of a measured stress similar to Pavlov's collision between excitation and inhibition, 3) measuring accurately the changed responses of the individual against his own specific norm. Since all dogs vary in what is their norm it is important to establish this for each animal.

Here again the CR measurements rather than the gross behavior furnish the criteria —viz., the changed relations between the excitatory and inhibitory, also between the strong and the weak CR's. The paradoxical phases, where the inhibitory CR's become partially or completely converted into the excitatory, are early indications before the observable behavior reveals deviations. We have seen this in our dogs before they develop an evident neurosis.

This method is dependent upon visceral measurements which I have developed in my laboratory in the past 19 years, viz., the cardiac CR's. The cardiac conditional reflex forms before the specific salivary or motor CR's and paradoxically it may outlast the specific. It is more resistant too. Since the cardio-vascular and respiratory CR's have different characteristics from the conventionally measured ones, it is necessary to say a few words about them. First the cardiac CR, as we have shown, is a more delicate measure than either the salivary and motor CR's established by Pavlov. The cardiac CR can also measure degrees of inhibition which cannot be done with the salivary or

motor responses. In general however the cardiac and the specific CR components are parallel. Important differences, on the other hand, appeared as our studies progressed over the years. Contrary to our expectation, the cardiac CR's form much more quickly than others, often after the first repetition, while the motor and salivary may not appear for 30-100 trials, requiring perhaps 4 or 5 days. Another characteristic of an opposite nature was seen: the salivary and motor CR's are readily extinguished by the cardiac which may last a long time—4 to 5 years or more.[4]

These differences I have called schizokinesis. This phenomenon explains why in a patient without external symptoms there may be violent internal responses especially seen in the visceral reactions, not only expressing organ neuroses but a general psychopathology. The degree of schizokinesis may itself represent a susceptibility to pathological deviation, and it has the advantage that it can be seen very early.

The more superficial conventional CR's will not always reveal this susceptibility—it is necessary to add the more subtle emotional measures (cardio-respiratory) which we have developed. The differences between the time of appearance of the visceral and the superficial CR's I have described with the term schizokinesis.[5]

Another aid in the ability to predict which animals will develop psychotic symptoms under stress is the recent advance in the basis for a classification into types with the help of chemical stimuli which has been developed chiefly in Bykov's laboratory. Casual observation or any other method of examination except the exact laboratory one of quantitative measurements do not reveal the susceptible animals.

This method of CR imposed stress has been used by me not only with dogs but in the psychiatric clinic with comparable results—viz. the psychotic shows in his CR record an entirely different record from the normal subject.[6] It is worth mentioning that one well-known psychiatrist considered normal at that time, gave the same response to my CR test as a psychotic (15 years ago); and he has recently developed into a full-blown paranoid schizophrenic.

At the present time we have carried this method much farther in the dog than in the human. We have been able to predict psychoses in our dogs; we have had one dog whose neurosis lasted 12 years and now have another (V-3) who has been catatonic for 9 years and observed by a number of psychiatrists.

A study of the CR function in each individual, and especially the cardiac CR, makes possible a rational application of drugs in prevention as well as therapy. Drugs vary in their effect with the individual.[7] In certain dogs of the inhibitory type we have found that meprobamate was very efficacious. Thus in V-3, a dog catatonic for 8 or 10 years, meprobamate relieved his symptoms almost completely, and transformed him from a dog that ran away or became catatonic whenever any person approached him, to a free animal. Alcohol which inhibits sexual reflexes in normal dogs, in V-3 changed impotence to potency.[8] The individual is an important element in drug therapy. A prediction of what drug to use can be ascertained by measurement of the cardiac responses in preference to the motor. Thus certain drugs eliminate the cardiac CR but do not affect the motor and vice versa.[9,10]

This method could well be used as a basis for a rational prophylactic psychiatry. Young children could be given CR examinations routinely in school or by public health physicians, especially those whose heredity or environment indicate the need, along with a physical examination, and according to the method described by me, subjected to an artificial CR stress. Appropriate CR measures would predict which ones were liable to develop psychoses later, and they could be protected by proper methods, including drug therapy. We have seen how certain new drugs seem to protect against development of cardio-vascular neuroses. The environment could be regulated to the individual as is done in those with incipient heart failure.

Summary:

The study of the individual by the CR method using precise quantitative measures, enables us to ascertain the type. Past work makes possible to say which types will suc-

cumb to stress (by imposing an artificial laboratory test) and become neurotic or psychotic. The inclusion of the cardiovascular responses and other visceral measures reveal this susceptibility to an extent that was not previously possible. Difference between visceral responses and the more specific superficial indicate a further special susceptibility (schizokinesis). The effect of bio-chemical agents and other modes of treatment can be gauged by the visceral reactivity as well as in the general behavior. With the means afforded by this precise determination of susceptibility to stress before a breakdown occurs, we have within our hands the basis for a rational preventive psychiatry. This has been proved successfully in the laboratory and with certain types of patients in whom recurrent psychoses have been prevented.

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Material Aspects of Mental Disease

RALPH W. GERARD, M.D.

For any behavior there must be some material substratum. For any change in behavior there must be some change in the material substratum. A nerve impulse can exist only when there is a nerve to carry it; and a change in the second nerve impulse, as the result of the passage of the preceding one, depends only on a change left behind in the nerve by the nerve impulse, not on a change directly from one nerve impulse to another.

Similarly, the functioning of the brain in general, which is behavior, must depend, in a broad sense, on the architecture of the brain. Any change in behavior whether induced by nerve impulses as the result of psychotherapy or by a changed chemical milieu as the result of pharmacotherapy or in any other way, must be associated with a change in the material situation. I have said nothing new so far, but am perhaps pointing out that "nature is a structure of evolving functions." Perhaps I am introducing an intervening variable, such as inhibition or excitation in the Pavlovian sense, which contributes nothing to the phenomena being described until the new correlate is analyzed further. The problem is, of course, to keep such a broad consideration from being vacuous, as Malamud well put it; and the way to keep it from being vacuous is to put in the particulars.

This means, especially I think, to ask at which level, which things are important. "Level," which no longer needs definition, includes the molecular level; the integrated, coordinated organization and functioning of molecules to give the cellular level; the patterned working together of cells to give the organ level; organs to give the individual; the individuals to give the group; and groups to give the society. (One can put in more levels if desired.) I think, in principle, that we will ultimately understand what happens at the social level in terms of individual psychology; individual psychology will be understood in terms of the gross behavior of the nervous system and of the interaction of neurones; and the way the individual synapse and individual neurone behaves will depend upon the population of molecules and other subordinate units that constitute it. It is, however, patently impossible, in the foreseeable future, to perform such an act of reduction; and it is pragmatically not desirable to do so in many cases. So that the real question, again, for each situation, is at which level is attack most profitable. Sometimes this will be at a higher level, sometimes at a lower one.

When do changes that occur in the system become irreversible and when do they remain reversible? I have heard Bevan over the radio and always wondered why such a distinguished and eloquent speaker had a speech defect—a peculiar sort of lisp as it seemed to me. I spent a week in Wales last summer and discovered that this was not a speech defect; this was English spoken with a Welsh accent. The attribute was not an individual but a cultural one. Nonetheless, although originally Mr. Bevan could have learned to speak any tongue in any form, I am sure that at this stage of his life he would be quite unable to speak, say, American English. Whatever the higher level sociopsychological factors that brought about this way of speaking, they have left a nervous system which today speaks that way and cannot speak otherwise—or we should not find so many intelligent people retaining a strong accent after decades of use of a different language in the country of adoption. It might be possible by hypnosis, by intensive psychotherapy (which means pouring nerve impulses in certain patterns), by light sedation, by I don't know what manipulations, to change these traces in the nervous system so as to cure this way of speaking. But I am not too optimistic that one can do a great deal about it after a person is grown up.

From Mental Health Research Institute, University of Michigan.

The author, for this paper, was awarded, jointly with others, the R. Thornton Wilson annual award for his contribution to psychiatric research and treatment.

Something can certainly be done at an experimental level. You will recall the work on chimpanzees raised in total darkness for the first month of their lives. Although the eyes and brain were unmolested, the animals never acquired the ability to use pattern vision. During the maturation process certain things, that should have happened in the nervous system as the result of functioning, just didn't happen. The nervous system developed in some other direction than in the normally guided one and it was then too late to re-establish the correct connections. Something very similar to this undoubtedly happens in the child with strabismus who suppresses one visual image. Here also time is of the essence. If the divergence from normal is caught at the beginning, one can correct it; later, it is irremediable.

So here at these higher levels, involving the psychosociological components, the primary problem is the kinds of patterns laid down between neurones. This involves synaptic fields, electric fields, chemical fields; I don't know which in detail, of course, but the interrelations and interactions of neurones at the cellular level account for behavior at the organ and individual levels. I have been so bold as to suggest that the neuroses probably constitute this type of disturbance in the nervous system while the psychoses are more disturbances at lower levels, with the molecules and the cells themselves out of kilter, quite aside from any defects at the interaction level. Let us turn to these lower levels.

When one blacks out in low oxygen or goes into hypoglycemic coma, or diabetic or renal coma, or goes into convulsions because of parathyroid hypocalcemia, or under sedative drug action, or when the functioning of the nervous system is grossly disturbed in a thousand other ways, it is perfectly clear that we are dealing with something not patterned in the fine sense that I have been considering. Here is a more general effect, hitting at the cellular and molecular level.

The examples that I have chosen above are secondary in relation to the nervous system, which is not the primary site of the lesion, but rather the victim of changes due to disturbances in other parts of the body in which it is one of the organs. (I shall consider more primary disturbances later.) Here the changes are largely unpatterned. True, there are marked differences from one disturbing situation to another; the whole nervous system does not rise or fall as a unit in its functional level. But you would probably accept the interpretation that these functional differences depend on simple quantitative differences—in blood supply, the blood-brain barrier, metabolic rate—and qualitative differences—in metabolism, architecture, connection—from one group of neurones to another; so that, although all cells are affected, certain ones show a particular effect much more easily or strikingly than do the others. Oxygen lack causes degeneration in the striatum; carbon disulphide destroys the caudate, streptomycin lesions involve the vestibular nuclei; acetyl pyridine knocks out the hypothalamus, hypoglycaemic convulsions start in the amygdala and hippocampus, so on and on. In each instance, if the disturbance is pushed a little further the rest of the brain goes too.

Here we have the more general cellular, molecular disturbances in contrast to the organ and individual ones. Where there is a patterned pathology, involving disturbed interrelations above the cellular level, the indications are for a patterned therapy, the kind available through psychotherapy or sociotherapy. We are trying to hit differentially into particular neural networks, even without knowing what they are. This must be the situation that justifies the lovely phrase describing some neuroses; "By the group have they been broken, by the group shall they be healed." Conversely, when disturbances are more general, at the cellular and molecular levels, the attack has also to be more general and at these levels and so more chemical or physiological. The latter is not now so convenient or practicable, although it is by no means excluded in the future. Certainly with the growing use of the buried electrode, which can deliver stimuli or produce localized lesions, and of the micropipette, for injection of chemicals, the hope remains that biologically it will prove possible to trace specificity down through the molecular level.

It is implicit in what I have said, that

speed in attacking any divergence from normal is of the essence. If one can catch the perturbation that is still functional and reversible before, through repetition, continuation and fixation, it has become irreversible and therefore structural, the better the chance of correcting it. This, of course, corresponds to the fact that the early and persistent experiences are most difficult to alter. As to just when one moves from a reversible change—as in increased adrenal cortex secretion or the appearance of a facultative cellular enzyme— to a maintained change has to be worked out in each particular condition.

If hamsters are allowed to learn a maze or to act to avoid danger, the conditioning situation being presented each day, and are also given electroshock every day, they learn practically on the normal curve if the shock comes several hours after the experience. But if the shock is given a few minutes after the learning experience, the same amount of shock and the same amount of learning now leads to no learning. Clearly, there must be an interval between impulses entering the nervous system and their leaving a relatively indelible trace. We have gotten the temperature coefficient of fixation time and we have studied the influence of some drugs on it. My interpretation is that an impulse must go round and round in a neurone loop for a few minutes in order to leave an engram. This would involve tens of thousands of repetitions over the same elements—enough to change a physiological response into a structural residue.

There is great variability in the time during which reversibility is still possible. Animals injected with hemoporphyrin develop severe behavioral changes and degenerative lesions of the nervous system. A third as much of protoporphyrin, the normal heme precursor (to which the hemoporphyrin is a metabolic competitor), will completely protect if injected as much as three hours after the hemoporphyrin, but is useless after five hours. Studies on phenyl ketonuria show that each correction of the diet is helpful, later it is not. Only early treatment can correct cretinism. Incidentally, notice that I am mentioning a number of hereditary diseases; it is possible to do something for such subjects, to achieve a considerable therapeutic success.

Fortunately, in schizophrenia there is much reason to believe that there is a relatively long period of reversibility. Whether we achieve really preventive measures or only restorative ones, at least it is possible over years or decades, rather than hours or days, to reestablish good functioning of the nervous system. A variety of maneuvers, all the way from Loevenhart's carbon dioxide inhalation, or insulin coma, or electroshock, or carbon dioxide in its newer use, to psychotherapy, or group discussion or putting a pile of dirt in the ward and letting the subjects play with it—whatever the appropriate one be in each case—can restore, at least for a brief time, the chronic burned-out schizophrenic to more or less normal function. So the neural apparatus has not been too irreversibly damaged in this sense. Of course, from a broader viewpoint, the brain probably is and remains abnormal throughout.

One could develop at some length a causal chain of events from disturbed molecules to disturbed behaviors. It is only in the present sense that my phrase which has had such a vogue, "No twisted thought without a twisted molecule," was meant. It is obviously changes in the functioning of neurones—whether they discharge or not, what their thresholds are, how long it takes them to recover from activity, how long the fixation process lasts—which immediately determines behavior; but this in turn is determined by their chemistry.

For example, consider the neurone threshold, which is related to the question of excitation and depression, to convulsive disorders, to coma. It is quite clear that the threshold of a neurone varies with the potential across its membrane. Further, at least in the case of muscle which we studied, and it must be equally true for nerve, the magnitude of the membrane potential varies regularly with the cellular concentration of creatine phosphate. The synthesis of creatine phophate, in turn, depends on adenosine triphosphate, which is formed by a series of enzymic reactions with the aid of energy from oxidations.

We were not surprised, therefore, to find

that audiogenic mice and rates, strains which are highly sensitive to sound and can be given lethal convulsions by, say, jingling keys, had a lower concentration of ATP in their brains than did normal related strains. Moreover, the sensitivity is greatest at around 30 days after birth, and it is between the third and sixth weeks that the development of ATP and its related enzyme lagged in the brain of the audiogenic animals as compared with normals. Just during the period of susceptibility to fatal seizures was there a low ATP, presumably a low creatine phosphate, a low membrane potential, a low threshold, and oversusceptibility to bursts of activity spreading through the nervous system.

I would have liked to examine in some detail the types of moecular changes in cells and the appropriate therapeutic maneuver for handling each. Time permits only some summary statements. We are concerned here with molecular morphology—too many or too few of a given kind at some particular place; or too many or too few altogether. The distribution of molecules or ions, especially of inorganic ones, which are not formed or destroyed in the body, depends on their penetration across boundaries, on their transportation, on whether they are given off or taken up by some other organ, and ultimately on their suppy in food and the manner of their excretion from the body. A disturbance at any of these levels—input-output, interaction between organs, or movement across limited regions within an organ and into or out of a cell—can alter the distribution. Indeed, the effect of an electric field on ion movements is crucial to the whole functioning of the nervous system. The way change in membrane permeability enables nerve fibers to conduct impulses, and the many changes in the relation between organs are also important.

All these interactions are obvious enough; more interesting, in a way, are the changes due to altered balance between production and destruction of metabolic intermediates. All substances in the body, except those that enter as such, are formed from other substances and are in turn changed into still other substances. If A forms M, and M forms B, what alterations can occur? Most common is some blocking of the enzyme-coenzyme mechanism that allows A to change to M or M to change to B. The former decreases the amount of M, the latter increases it. Much effort has been directed to finding out, in particular cases, which is involved. Actually, there is always a chain of increases and decreases, so the difference is not so sharp as it may seem. Decrease of M may block some other reaction and lead to excess of X or deficiency of Y, and increase of M might do the same, and so on.

Many emphasize the accumulation of some blocked intermediate. My own strong impression is that we end up sooner or later with a deficit of something. Suppose we accept that the ammonia increase in hepatic disease causes coma; the question remains how does ammonia do this? Similarly, how does phenyl pyruvic accumulation lead to the oligophrenia? Each acts on some other metabolic link, and could increase or decrease other substances. It could speed, divert or block reactions, so that an almost unlimited matrix of chemical-metabolic interactions is possible.

Each case must therefore be analyzed before a rational treatment for it is clear. Yet, if one clear step is the accumulation of a particular substance, any maneuver to prevent its accumulation—by withholding its source or blocking its precursor—may solve the problem. And if the deficit of a particular substance is a clear link in the sequence, supplying this missing intermediate may correct the trouble. This is frequently the case in genetic defects—as in neurospora mutants or human cretinism. Finally, the blocked catalytic mechanism, the enzyme and coenzyme system, might be restored so that the metabolic flow is restored to normal.

All these are possible. The biochemist is rapidly filling our test tubes with the critical components of living catalytic systems. The main problem is to get them into the cells, where permeability is so limited. Even on this score, there is encouragement. The blood brain barrier, for example, normally will not let in glutamic acid, but when it is disturbed as the result of hypoglycemia, glutamic acid does pass. Proteins do cross cell walls, and many conditions—hypoxia, hypoglycemia, drugs—favor their passage.

So the situation is by no means an impossible one.

I mention these items because, I think, the tremendous feeling of empathy of the physician and therapist with the patient has colored judgment about mental illness. The doctor has felt that any disease due to an hereditary organic defect is hopeless and therefore he preferred to emphasize other factors. I submit that there are many hereditary metabolic defects for which more can be done today than for some of the unidentified or even identified determinants of behavior. It is easier to correct an infant's cretinism than an adult's accent. Something can be done about these metabolic errors and two examples will point up my position.

One is phenylketonuric oligophrenia. In our own lifetime, over the couple of decades since the disease was recognized, it has moved from the great unknown to a precisely known and reasonably manageable disturbance of the nervous system. Fjolling first noticed a color reaction in the urine of certain feebleminded children and related this to phenyl pyruvic acid. This phenylketonuric oligophrenia is hereditary. Further work showed that phenyl pyruvic acid in the blood as well as in the urine is high, and that in the blood not only phenyl pyruvic acid is high but also phenyl alanine, the amino acid which gives the phenyl pyruvic acid on deaminization. Phenyl alanine is normally changed to tyrosine by putting oxygen in the molecule. These patients, when loaded with phenyl alanine, could not increase blood tyrosine as the normal does, but simply accumulated phenyl alanine. There was clearly a block somewhere in the oxidation of phenyl alanine to tyrosine. Biochemists worked out the mechanism of this reaction; phenyl alanine plus triphosphopyridine nucleotide (TNP) plus potassium plus a coenzyme plus two enzymes constitute the active system. In the phenyl pyruvic subjects there is no decrease but an actual increase in coenzyme, and TPN and potassium are present. Clearly it is the enzyme that is lacking. Further, of the two enzymes involved in the one present in the liver proves to be lacking.

Thus, a disease that started as a form of feeblemindedness has become an inherited metabolic error involving the lack of a specific enzyme in the liver. Moreover, there is some evidence that feeding phenyl pyruvic acid to animals, raising the blood concentration to levels that appear in humans, interferes with their learning behavior. So, Whatever the secondary mechanism may be, here an excess of a specific substance can bring about the important symptomatology. Cutting down the excess should be beneficial and the ideal way would be to get the missing enzyme back into the cells and keep it there. Maybe this will become possible but we are not up to it yet. What has been done is to develop diets which contain minimal amounts of phenyl alanine. This is effective since the substance is not made in the body; it is one of the essential amino acids. Current clinical reports indicate that children put on this diet sufficiently early get along much better than otherwise. If given phenyl alanine for a while they deteriorate rapidly and improve again when it is removed.

The other example of my thesis, schizophrenia, has not yielded such concrete biochemical results. Here, we still need a definitive criterion, like the urine color test, to give greater nosological definition. I am not going into the evidence for believing that biological and hereditary factors are important. Everybody knows Kallman's work. When I first began to talk about it I found but few psychiatrists who knew it and most did not believe it. Bodily differences have been described and related to behavioral differences—sluggishness of response, poor reaction to stress, "stenosis" of behavior (a term I use as particularly descriptive), and so on and on. But we will not be on safe diagnostic ground until there are reliable objective criteria. Whether they be biochemical, physiological or behavioral makes no difference. The material ones are more easily objectified and "sold." I will just remind you of some at present on the horizon. And I might as well say now that every one of these, at least those on hand long enough for checking, has been rejected by some investigators.

Substances specific to the urine of schizophrenics, isolated chromatographically, when injected into rats markedly interfere with their rope climbing performance. Patients have been controlled as to diet, etc. Schizo-

phrenic blood injected into rats also interferes with their speed in climbing a rope. We, as others, checked that and got nowhere. Yet Dr. Winter, who developed this test and is scrupulously honest and careful, assured us at a recent conference in Strasbourg that he had been highly successful in diagnosing patients by blind runs on blood sent him from three hospitals.

Schizophrenic blood has also been reported to facilitate the blood pressure response to local application of adrenalin to the rabbit cortex. We are testing this now.

There are reports that the ability of insulin to increase the glucose utilization of isolated rat diaphragm is prevented by schizophrenic plasma; and indeed some Norwegian workers find an alpha globulin which specifically combines with the insulin. This finding, reminiscent of Meduna's early claim of anti-insulin action, is also being examined.

Early reports on changes in the phosphate turnover of red blood corpuscles from schizophrenics, were extended by Boszermeny-Nagy, working in my laboratory at the University of Illinois, and Gerty, who showed a difference in insulin effect. More recently Gottlieb's group showed greater changes in phosphate turnover under an emotional or insulin stress in schizophrenics than in normals. Dr. Ling and I are finding a consistently greater amount of a nucleotide in schizophrenic corpuscles than in normal ones, but the full controls are yet to be completed.

As I have said, for every positive report there have been counter reports, and even when the findings are real they may not be due to the disease schizophrenia but to all sorts of secondary factors. An obvious example is the decrease in some phenolic acids in the urine of schizophrenic, as shown by several workers. This has now been proven conclusively by Kety's group to be the result of less coffee drinking. The substances are metabolites from coffee, vary with the coffee intake, and are low in schizophrenics because they drink less coffee.

There is much smoke; we have yet to see the fire. But I have every confidence that with advance of the life sciences we will soon see some flame, just as I am confident that advance in the physical sciences will soon show us things we have not previously been able to see. Whitehead once told me a quatrain, attributed to a cook, which ran as follows:

"Moon, lovely moon, bathed in fire sublime,
Careening throughout the far boundaries of time,
Whenever I see thee I ask in my mind,
Shall I never, oh never, behold thy behind?"

Discussion

Dr. Furst: I would like to ask Dr. Gerard to comment on monamine oxidase and its relationship to emotion and primary depression.

Dr. Gerard:

First, manic and hallucinatory states were attributed by Canadian workers to the accumulation of abnormal or excessive oxidation products of epinephrine which lowered neurone thresholds. When this was questioned, the New Orleans group said the catecholamines were not increased but the enzymes that oxidize them were different in schizophrenics, so that oxidation was slower or due to abnormal products, and so on. National Institute of Mental Health workers recently reported no difference in these reaction rates or products in schizophrenic plasma. They even offered evidence that adrenolutin, adrenochrome, and the like are not in the normal path of metabolic breakdomn of adrenalin or nor-adrenalin. Nonetheless, it is not often possible to explore the total conditions under which processes occur. Abood, indeed, offered evidence that adrenochrome is formed from the catecholamines when oxidized by ceruloplasmin rather than by monoamine oxidase; and so on and on—without entering the serotonin arena.

I also am guilty of putting forward an hypothesis involving the catechols. Adrenalin certainly can lower the thresholds of neurones. (It can also raise thresholds and inhibit in larger amounts; but we showed conclusively for the motor cortex and elsewhere that application of adrenaline increased excitability.) It is nice to think of a possible modulation of neurone thresholds throughout the brain, depending upon the level of circulating adrenalin, as well as on the activity of the reticular formation. This is a kind of extension of Cannon's emergency theory of epinephrine liberation, to include effects not only on the soma but also on the brain, on the level of the tension of the psyche. It is a long story, but the amino oxidases may help determine what happens to the adrenalin liberated, whether other stimulating compounds are formed, and the like.

Dr. Azima: I would like to make one point and ask Dr. Gerard two questions. If your philosophy is reductionistic my impression is that in the present state of epistemology this implies the fallacy of infinite regression and this fallacy is based upon two other fallacies. One is the fallacy of misplaced concreteness and the other one is the fallacy of linear causality. This means if anything affects B then it affects C and so forth.

Dr. Gerard: You are perfectly correct. I meant to accept positivism. I am aware of all of the difficulties you raise but I still cannot think otherwise than in terms of cause and effect. Neither could Einstein.

Dr. Azima: The second question I want to ask, do you believe in the concept of linking and in the concept of emergence?

Dr. Gerard:

I think very few would be interested in pursuing this very far. If you have not seen it, may I commend to you the April issue of Behavioral Science. This monograph, also separately published by the National Academy of Sciences, on "Concepts of Biology" is the report of a three day symposium in which a dozen leading biologists participated. Many of these issues are discussed and I had the responsibility of preparing the preliminary organizing article and the final summary, so my views are available there.

Specifically as to emergence, my view is that there is no emergence, in the sense of some super natural aspects appearing with new combinations. But with every additional level there are new kinds of relationships possible and some are not directly extrapolatable from the older ones. A square equation does not give the mathematics of a cubic equation. However, having seen the more complicated situation one can always understand it in terms of the interrelations of simpler ones. It is just too big a job intellectually to consider all the variances possible in going up levels; whereas it is relatively easy to come back down and to develop the understanding that gives predictive control. This is what I would equate with the term causality, to avoid the philosophical problem. I think that, sooner or later, one must get to the micro level for control; but first many relations must be established at the macro level. I do not say that sociological, psychiatric, psychological, or neurophysiological formulations are not good because they are not down to the molecular level. As to infinite regression, as long as the physicists are giving us subnuclear and smaller units, I am willing to regress too.

Dr. Gerard, in response to Dr. M. K. Opler:

I thought I was going to be able to say I agreed with you and stop, but your last sentences indicate an area of conflict. Our philosophical orientations seem to fit well until we come to grips. I think of the story of the man explaining socialism, who said, "If you have two yachts, that means you keep one and give me one."

"Yes, that is clear."

"If you have two automobiles, you keep one and give me one."

"Yes, I agree."

"If you have two shirts, you keep one and give me one."

"Wait a minute! I *have* two shirts."

We agree in principle all the way until it comes to schizophrenia and the question of how much is horse and how much is rabbit. Here, I think, each of us is expressing a faith. At this stage we don't know the answers; if we did know them, and are rational beings, we could not argue about them. It is because so much is still unknown that my judgment, on looking over the total evidence, can be that the biological component is a larger one, yours puts the weight more on the social level.

Dr. Opler: You seemed to when you said the others are concomitant variations. In any event, if you don't we have no disagreement. The only difference this judgment makes is that it determines where one puts his chips, how he will direct his research effort to solve schizophrenia. The one thing you said that I would vigorously disagree with, and maybe you will disagree with it yourself if I paraphrase what I thought you said, is that all these factors enter and that it is meaningless to try to analyze further.

Dr. Gerard:

Good. Then I am not disagreeing with you. This is the same thing Malamud said. Granted that there is a heredity and an early embryological development and a past group experience and a current life stress—a mother-in-law coming to dinner or whatever it is. Granted that all these factors enter, one gets no further unless he asks; so far as this particular variation is concerned, to what is the variance attributable, how much to this, that, and the other factor. The answer is a matter of experiment and what we are all seeking.

I am reminded of my friend, I can say "friendly enemy," Mortimer Adler, with whom I have often crossed swords. He loved to give a sweeping talk and point out that science did not face the grand questions of the universe; only philosophy could face them. I would then point out that science did not as yet answer, and perhaps never asked, the grand questions of philosophy; but science does answer the questions it asks and philosophy does not. So let us hope that science gets around to them!

Dr. Marvin K. Opler:

I find myself much interested in and curious about this last flurry of discussion. Various positions are described and criticized, but it seems to me that the criticism must be more specific than it appears when we merely talk about the general history of science. I might say that as an individual, Dr. Gerard has a right to regress, as he laughingly puts it, and to conduct his impressive research at any point along the line of regression he chooses. I have no fear that he will be involved in his own work in infinite regression or even with what the Freudians call regression. However, both of the preceding speakers, in their disagreement, have each commented on the general history of science. And I think it is high time to leave that generalized argument and to talk about social and preventive psychiatry, which is the scheduled topic of this meeting. The thing that bothers me is not the reductionism, as was just suggested, but rather what that reductionism implies about the direction of research which Dr. Gerard, somewhat cavalierly, insists must begin on an organicist level.

Those who insist we begin on any one narrow level, whether it is simply the organicist level, or among other thinkers the "purely psychological" level, are guilty not only of an insistent reductionism as suggested here, but also guilty of an attempt to split apart relevant aspects of research. The human problem, for instance in schizophrenia, neither begins nor ends on the organic level. The human condition or "human predicament," as some French existentialists have called it, is by definition not something that can be understood by separating the different approaches and going on from there. The organicists, if they are fervent purists, study such conditions as schizophrenia, alcoholism and other highly generalized or presumptive illness entities by such a segmented approach. Their assumption always is that you will reach important conclusions on one level or another. But we all know that schizophrenia is not a unit psychosis, that alcoholism is not necessarily an illness entity, and that both may develop in a framework of socially or culturally derived stresses and strains which affect persons of widely different organic make-up. The assumption that you always hit "pay dirt" on one level or another disregards everything we know to date about the etiology and dynamics, and the over-generalized character of our psychiatric nomenclature for these disorders.

Incidentally, I entirely agree with Dr. Gerard's diagram of levels, but so far as the human being is concerned and so far as the psychiatrist's effectiveness is involved, I would insist with him that these social, cultural, psychological, and organic levels are always interrelated. To say they are not interrelated is to become mystical and insist upon a dichotomy of mind and body. But Dr. Gerard wishes to say, on the one hand, that there is not a separate development of such levels, and then wishes to add, on the other hand, that one will arrive at the neatest experiments and the most revealing data only on one level (the organic) and through attention or application to that one level alone. He seems to me to contradict the first proposition when he adds his second proposition.

To say that success will be achieved on one level only is naive when we look at specific discoveries in the general history of science. For instance, the discoveries about pellagra, beri-beri, and such deficiency disorders as kwashiakor were very useful to psychiatry. In these examples, there is a link between a specific disease entity and an organic system of causality. The same is true of toxic psychoses and such scattered examples of the organic disorders as Korsakoff's syndrome. I was always impressed when I read the original documentation of Dr. Alfred Hess and others on vitamins. Everyone knows that Hess found out about deficiency situations affecting New York school children by learning something about their social status and ethnic group background including what they ate. He was interested in knowing in what population rickets had a high incidence. This is what led to the biochemical and other research. Dr. Walsh McDermott is currently studying the epidemiology of tuberculosis among a population of Navajo Indians to achieve the same kind of initial insights in regard to alarmingly high incidence rates.

To cite an instance, concerning the epidemiology of a non-organic condition, the Puerto Ricans in New York City and New York State have high rates of schizophrenia per capita according to Malzberg's published data. In my own epidemiological studies in this group as reported for an area of the Eastside of New York City, we found that Malzberg's data, if anything, had probably understated the case, for we encountered considerable numbers of ambulatory schizophrenics. Malzberg's is of course a study of treated prevalence. We studied not only treated cases but also Puerto Ricans who had never been in treatment, so that we had a prevalence study of both the treated and the untreated. Besides the epidemiological surveys in this group, we decided to study Puerto Ricans who were hospitalized because of schizophrenic disorder. We also studied neurotic Puerto Ricans who appeared in a randomly sampled population. Some people claim that neurotics do not develop into full-blown psychotics, but my colleague, Dr. Thomas Rennie, earlier proved that this was not the case and that concepts about the unit psychosis were extremely dubious. We found a continuum of stresses and strains upon the Puerto Rican population which in some cases led to neurotic behavior and in others to a case history where psychoneurosis had grown out of a florid neurotic background.

We also found "well" Puerto Ricans. But how were we to explain the greater prevalence of mental disturbance in this population when compared with other ethnic groups of New York City? The answer is that the normative community, the social and cultural backgrounds of Puerto Ricans in New York City, and their typical problems were used to produce hypotheses which we could test in samples of hospitalized Puerto Rican schizophrenics. These hypotheses were best called biosocial. They necessitated joint research by social scientists, social psychiatrists, and psychologists. Ideally one would add on neurophysiological and biochemical research. But neither neurophysiological nor biochemical research will necessarily tell us anything about why Puerto Ricans have more schizophrenia in New York City per capita than any other group. Further, their problem is not merely a neurophysiological and biochemical problem. The definitions of a life process like schizophrenia require us to include the social and cultural strains upon a population that are reflected in epidemiology and which, even if they have neurophysiological and biochemical correlates, are problems which do not in any sense begin on such organic levels.

Research, Theories, a New Test and Medical Writings

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Convergence of Psychodynamic and Physiodynamic Approaches in Psychiatric Research

JOHN D. RAINER, M.D.

In all ages, as far back as the ancient times of Hippocrates, physicians have sought to view man as a total biological entity. The holistic conceptualization of clinical case histories, obtained by conscientious doctors at the bedside of their patients, paralleled the stage of advancement made in a given era in "the search for the nature of disease."[23]

One of the most promising steps forward in this development was the shift from the *ontological* concept of disease, considering a certain type of illness as an autonomous entity endowed with a natural history, to the *biographical* approach to disease. From this point of view, disease is regarded as a *dynamic* process that "develops across time in the patient's life."[23]

In psychiatric thought and research, the dynamic conceptualization of ill health has been hampered by the tendency to separate it into psychodynamic and physiodynamic patterns of approach. Philosophically, this type of division is as old as Descartes, if not Plato. Except for the early Greek naturalists, or such isolated thinkers as Spinoza and Santayana, or those working close to the practical sciences, the divided approach has permeated the various schools of thought up to modern times.

In the history of psychiatry, this dichotomizing trend may have resulted, at least in part, from unevenness in the rate of advance of different techniques and unifying principles. At any given time or place, certain areas were more highly developed and offered more sophisticated theories and methods than others. For example neuropathology, bacteriology, and psychology followed one another in holding sway. Moreover, such pioneers as Kraepelin and Freud deliberately turned away, for a while or even for a lifetime, from one approach or the other because they were not convinced at the time of having sufficient knowledge for its productive application. In fact, such onerous decisions were often made by scholars who had a thorough foundation in the very areas they chose to neglect.

Although quite familiar with the backgrounds and potentialities of approaches other than their own, these men considered it unwise at a particular time to give another method their attention. They had to take this seemingly arbitrary course lest they or their less disciplined colleagues dilute their research, thus falling short of the important discoveries that might follow from the concentrated pursuit of one avenue of thought. Today, of course, we are charged with the task of amalgamating the essential components of their diverse findings. Nevertheless, there is no reason for minimizing such singleminded devotion. It is only the uncritical perpetuation and sterilizing petrification of such systems that are to be deplored.

In surveying the development of modern psychiatry, one finds various efforts, such as the psychobiology of Adolf Meyer, to synthesize divergent concepts. However, most of these efforts were premature from the point of view of research, because the state of knowledge in the physiological and chemical disciplines, on the one hand, and the specifically psychodynamic approaches, on the other, was not suffciently advanced.

Since then, however, the biological sophistication of psychiatric research workers has increased and technical advances in the various scientific disciplines touching on the problems of mental health and disease helped to break down time-worn compartmentalizations and prejudices. At long last we are in a position where the use of a unified biological approach can be rendered more than lip

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From New York State Psychiatric Institute, New York; Research Associate in Psychiatry, College of Physicians and Surgeons, Columbia University, New York.

The author, for this paper, was awarded, jointly with others, the R. Thornton Wilson annual award for his contribution to psychiatric research and treatment.

service. Not only have refinements been made in the physiological sciences, but the techniques of psychodynamic observation and interpretation have been considerably improved.

The current trend toward combining physiological and psychological procedures in modern psychiatry will be illustrated here by viewing it from the standpoint of one particular interest which would seem to lend itself rather well to this purpose, namely, medical and psychiatric genetics.[31] Patently, any comprehensive concept of the human organism in a temporal framework is bound to begin with the fertilized ovum and the potentialities contained therein.

In this context, one discovers at once how spurious are the attempts to draw a dividing line between physiodynamic and psychodynamic—between the dynamic of growth and adaptation determined by changing nuclear, cytoplasmic, enzymatic and anatomic forces and that determined by the changing constituents of neural, hormonal and total behavioral responses. From its earliest formulations, genetics always made this point, thereby foreshadowing the present unifying scheme.

With the organism growing in complexity as it evolves from its zygotic origin, our methods of studying it have had to become specialized to such an extent that they may seem far apart. Nevertheless, the various investigative approaches are sure to converge at some point. The converging pattern becomes clear at the level where explorations can be focused upon the biological organism with its evolutionary potentialities and its adaptive process traceable throughout its career.

Of course, various methods exist for portraying the human individual. Man may be viewed phylogenetically; that is, as a product of biological evolution representing a complex form of matter able to adapt and create. Ontogenetically, he is a developing anatomical, structural, chemical organism. From the standpoints of ecology, demography and sociology, he is a member of a human society in a complex natural and social world. Naturalistically, he is a biographical entity observed by his contemporaries or successors. Poetically, he may be thought of as a stream of subjective experience, conscious or unconscious. There is no way of telling which approach to man is predominantly physiodynamic and which psychodynamic.

Only one thing is clear. There is no respectable scientific concept today which does not include *time* as its most important dimension, and *change* as its most important phenomenon. Connoted as they are in the very term *dynamic,* both these factors are common to the two theories calling for integration. Here again, there is a point of convergence in the science of genetics, and a few remarks about the foundation and direction of modern genetic theory may be in order.

Two main periods may be distinguished in its development—the statistical and the physiological. The first is largely descriptive, special and static; the second is more general, explanatory and dynamic. Although pertinent observations had been made previously, it was in 1865 that Gregor Mendel reported on his crucial garden pea experiments and ushered in the statistical era.[24] His observations of the "unblended" separation and subsequent recombination of stable units, confirmed in 1900, led to the first description of populations in terms of the frequency and distribution of types on a genetic basis.

Proceeding from the premise that single characters behaved as if determined by paired particles in the germ plasm (later called genes or alleles), a study of the results of various types of mating confirmed the expected statistical ratios for both phenotypes and genotypes in the next generation, the results differing according to the dominance or recessiveness of the gene in question.

More recently, many geneticists inspired by Goldschmidt's work came to regard the statistical or "hyperatomistic" viewpoint in human genetics as too static. Its main weakness was seen in the fact that more and more entities (such as modifier genes) were needed to explain the complexity of genetic adaptation. Incidentally, similar difficulties were encountered by nuclear physicists in an entirely different field of endeavor.

It was fortunate indeed, and certainly

more useful for purposes of psychiatric research, that discovery of the chromosomes[34] and subsequent identification of many of their chemical functions within the cell nucleus gradually led to a broader physiological or dynamic conception of genetic phenomena. While accepting the basically statistical tenets of genetics, the new emphasis was placed on an understanding of variations in physical and mental health in terms of genic action and developmental systems.

In this scheme, attention could be paid to the phenomena of interaction, embryonic regulation and integration, rather than to an endless search for explanations "in terms of unproved, additional systems of units for more and more genic permutations."[13] Genes came to be considered in time as clearly differentiated regions or loci with all the necessary properties of regulation and self-duplication.

On this basis, the field of action of modern genetics may be extended beyond its classical boundaries. Among its functions may be listed prediction of the potentialities of the offspring of individual matings, prediction of future population trends, exploration of the phenomena of evolution, and the eugenic goal of maintaining the health of individuals and populations.

The new dynamic concepts make it possible for genetic theory to include within its scope the balanced interaction of normal human function so closely related to the phenomena of health within a social group. It may still be true that "mutants which affect general features like growth, fertility, sterility and viability, cannot yet be isolated and localized like the standard mutants of elementary Mendelism."[14] However, a sufficiently broadened theory will enable the discipline of genetics to make its contribution not only to the analysis of rare pathological traits but to all aspects of human existence. It is this conception that may serve as a unifying frame of reference in psychiatry.

Of course, whenever genetic theories are applied to psychiatry it has to be borne in mind that they are essentially dynamic in nature. According to Kallmann, unusual behavior should always be viewed *"as an extremely complex and continuous chain of events in the individual's adaptive history, rather than the automatic expression of a fixed congenital error in metabolism."*[21]

Moreover, note should be taken of the admonition implicit in recent statements by both human geneticists,[1] and psychoanalysts.[29] The gist of these statements was that any effect produced by a mutant gene comes within the scope of human heredity, whether it be an enzymatic disturbance or an inherent lack of ability to respond to certain environmental stimuli with a normal type of behavior.

Actually a disordered behavior pattern may, in some instances, stem even more directly than a correlated anatomical defect from the postulated change in primary gene action. If this theory is correct, the *demonstration* of anatomical or chemical correlates would no longer be an essential stipulation for inherited behavior patterns, since the latter characteristics may have a gene-borne evolution of their own. A sufficiently precise psychodynamic description may then serve as the basis of genetic investigation.

Fortified with such a genetically oriented scheme, we can examine the convergence of psychodynamics and physiodynamics in theory as well as in practice. It is widely accepted that psychodynamics, however individualized in its practical application is basically the science of motivation and control, whereby human behavioral variations are analyzed in the particular (gene-specific) context of the organism.

In its modern form, psychodynamics contains the concept of an effector system, variously called conflict-free ego, action system, or executive function. The task of this system is to satisfy biological needs with due respect for the realities of surrounding personal and natural environments. Both the relative strength of the various biological needs and the characteristic mode of operating of the effector function were assumed by the originators of psychoanalysis to have primary hereditary components. In Freud's words, "every individual selects only certain of the possible defensive mechanisms and invariably employs those which he has selected."[10]

The primary role of psychodynamics as a research tool in a unitary biological approach is to uncover behavior problems

which await their exact solution from physiology and genetics.[30] This assignation in no way minimizes the importance of psychodynamic attention, whether it be done by classical methods of introspection, free reporting and dream analysis, child observation, or controlled experimental situations with humans and animals. As Jones predicted some 30 years ago, by these methods "one is enabled to dissect and isolate mental processes to an extent not previously possible." Inevitably, such procedure "must bring us nearer to the primary elements, to the mental genes in terms of which genetic investigations can alone be carried out." In other words, "the next study to be applied would be one in the field of heredity".[17,18]

This trend becomes clearer when one considers the various schemes of psychodynamic classification, from early descriptions such as neurasthenia and hysteria to the current method of making diagnoses in terms of psychophysiological, psychoneurotic and personality disorders. It can be seen how the development of more refined diagnostic classifications in the group of nonpsychotic disorders was facilitated by increasing psychodynamic insight. This improvement in turn is a prerequisite for genetic and physiological analysis.

A brief review of recent collaborative efforts will substantiate the great ferment that is taking place. In these undertakings, contributions are being made by clinical psychology and psychopharmacology, as well as by neurophysiology, neuroanatomy and clinical biochemistry. Personality inventories and projective tests provide profiles of psychodynamic potential.[15] Differential responses to autonomic drugs are used to divide persons into differently reacting categories,[12] with psychotomimetic agents performing a similar role in the diagnosis of more severe disorders.[5]

Conditioning patterns, measurable electrically[27] as well as by more classical learning experiments, have been related to psychodynamic types on the one hand[8] and to variations in brain chemistry on the other.[22] Self-stimulation experiments with implanted electrodes have been used to define the anatomical and pharmacological basis for drive.[28]

One current hypothesis aims at linking certain findings regarding the action of tranquilizing and hallucinogenic agents by postulating mutually antagonistic centers in the brain, analogous to sympathetic and parasympathetic systems.[2]

Finally, determinative studies of gastric enzymes,[25] sex hormones and certain blood groups[4,6] seem to connect susceptibility to psychosomatic disorders with primary differences in these substances.

Searching for analogies in former eras, it would appear that many of these differentiating schemes are reminiscent of typologies dating back to Hippocrates and Galen and more recently to Pavlov, Kretschmer and Sheldon. As our science progresses, we may indeed be approaching a new "humoral" theory recalling the sanguine, melancholic, phlegmatic and choleric types of the ancients, or reaching a modern electrophysiological explanation of Pavlov's diversified dogs.

Be that as it may, more precise identification will make it easier than was possible with the older typologies to subject the differences found by modern research tools to genetic analysis. Thus, as Freud foresaw, we may soon be able to "divide the causes of neurotic disease into those which the individual himself brings into life, and those which life brings to him—that is to say into constitutional and accidental."[9]

Indeed, since no psychodynamic formulation denies that individuals in large measure select and create their life experiences, it would seem to be an oversimplification even to refer to accidental causes. Only in the frame of combined longitudinal and cross-sectional population studies will it be possible to bring to fruition the efforts of physiological and psychological analyses.

It is reassuring that the formation of hypotheses regarding the complex interaction of genetic, physiological and psychodynamic forces need not depend on random insights, however inspired. It is true, of course, that breeding experiments and environmental manipulations, such as used with increasing productiveness in the behavior analysis of dogs[32] or drosophila[16] are not applicable to humans. However, there remain three methods of systematic approach which can be applied in combination with new techniques in

psychiatry and its related disciplines, including those already described.

The first area in which the prospect exists of deriving a total picture of human functioning is the study of the process of development in infants and children. Without disregarding emotional factors, the total biological interaction between child and mother from the prenatal period on is currently being scrutinized.[3] What is more, increasing attention is being paid in these studies to the concept of individual differences among infants, whether in terms of sleep, feeding and sensory responses[7] or in those of activity types[11] motor behavior,[26] and specific reaction patterns.[33] The next logical step, and a much-needed one, in studies of this kind will be to correlate biochemical and genetic analysis.

Eventually, the collaboration between the disciplines of psychodynamics and psychogenetics will provide the most complete insight into normal and extreme variations in human behavior. In such a scheme, longitudinal family studies and comparative twin research with techniques from depth psychology are bound to produce refined psychodynamic and population data in all areas of psychopathology.

Another focus of convergence in contemporary psychiatric research is the area of demographic and sociological investigations, sometimes referred to as epidemiology. Studies of this kind are directed toward relating the frequency, distribution and patterning of mental disorders in a given population to its life conditions, and the main objective is to determine the differentiating effect of various outside factors on the origin or clinical symptomatology of properly defined disease entities.

Of course, outside influences react upon the individuals who make up a population. Just as the nature of the germ plasm is part of the study of any individual or family, so the genetic composition of a population must be considered when surveying a larger group. The various physiological and psychological factors have to be converted into their equivalent terms in population science—gene frequencies, public health level, and sociological phenomena. Such influences as assortative mating and differential fertility, migration, the effects of small populations, or the phenomena of mutation and selection play a decisive part in changing the frequency of gene-specific variations.

Regardless of whether it is the primary aim of any given population study to discover genetic patterns, investigate adjustment levels, or determine the frequency and type of some disorder, it is always essential to work with a representative population frame. An adequately randomized sample is needed if the total group cannot be studied. Apart from being uniquely useful in many other ways, one method of choosing a population sample is the twin study method and its elaborations,[19] which forms the third framework for collaborative research.

Comparative data are obtained in six dissimilar sibship groups related to a representative set of twin index cases: one-egg twins, two-egg twins of the same sex, two-egg twins of opposite sex, full sibs, half sibs and step sibs. This procedure provides a unique opportunity for investigating intra-family variations, especially with respect to traits that present complex sampling problems and require comparisons in both cross-sectional and longitudinal directions.

Carefully conducted twin studies, as well as their counterparts in the general population study area, have provided the lead in establishing the biological nature of the major psychoses, and thus have served to define another area of productive research for new generations of scientists. Unless one wishes to claim, for example, that being the identical twin of a schizophrenic is an accidental or "environmental" phenomenon, and indeed the only constellation certain to result in becoming schizophrenic over 80% of the time, one must respect the biological implications of twin study data.

Although the study of one-egg twins has the procedural advantage of keeping all known genetic factors constant, it is clear that enumeration of frequency data among twins will not of itself provide clues as to etiology. However, like any other family investigation, twin research can be readily extended, especially when one discovers one-egg twins discordant for a particular form

of disordered behavior. By means of systematic twin family studies, therefore, a researcher may hope that one of these days some very important findings will drop into his lap.

Among the innumerable determinants conceivable in a total biological approach, comparative studies of cellular reaction, endocrine function, protein synthesis or interpersonal development may be most fruitful. Intensive chemical analysis or intensive psychoanalysis of both members of selected discordant twin pairs may provide illuminating hypotheses.

In evaluating the findings in such cases, it would be necessary to consider the possibility that a "spiral-like development toward marked behavioral dissimilarity"[20] may arise not only from postnatal influences acting upon the twins, but in the prenatal or even chromosomal stages of development as well. Here we encounter such still poorly understood but experimentally verified genetic phenomena as penetrance and the action of suppressor genes. On the whole, it is not too much to say that the fascinating research method provided by twin study is bound to point out the need and inspire the quest for more knowledge in all the convergent fields bearing on psychiatric research, including genetics, chemistry, physiology in its broadest sense, and psychodynamics.

In closing this discussion on the convergence of physiodynamic and psychodynamic approaches in psychiatric research, it may be in order to make a few remarks about the effect on therapy of a unified viewpoint. It should be clear by now, if it was not five years ago, that the implications of a total biological approach would not lead to therapeutic nihilism, but rather to a well-founded optimism on the part of both physicians and the public.

The effective combination of "physical" and "psychological" methods of treatment is but one practical result. It is of even greater importance that the physician would have an opportunity to individualize his therapy and adapt it to the particular needs and potentialities of each patient within his own family and community setting. Finally, it is agreed that a physician cannot describe a patient if he knows only a part of him. The psychiatrist in particular, who is disinclined to preserve clinical blind spots, can only welcome a truly synoptic approach.

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Discussion

Dr. Harold H. Berman:

There are a few questions which arise in my mind on genetics and the chromosomes so-called and the genes. Do we, as the author points out, study genetics dynamically?

Before I went to Willowbrook I accepted all these facts and theories and suppositions but as we began to admit more and more infants and began to see more and more clinical syndromes which must have happened at a certain time in the development of the embryo, then, as the author points out, the environment and the sociological factors of the total population must be studied.

We see babies coming in with webbed fingers, deformities throughout the body, which must have happened at a certain critical period.

Then we began to investigate certain conditions. We proved that German measles in the first trimester can produce certain situations. Why? Then we went on to prove to our own satisfaction that German measles can be transmitted from one to another without symptoms.

Now working in the same way with infectious jaundice, these things occur in the environment. Other mothers that were carrying these babies were exposed to infections. Do we ask ourselves is it heredity? What happens to the genes after the ovum becomes fertilized?

I think as psychiatrists we must point the way, including genetics, to that rare physician who is not created yet, the prenatal pediatrician.

Dr. Rainer: I agree that any theory must include the complete development from the zygote through the prenatal and the post natal period; environmental forces act upon an individual who started out as a certain set of genetic potentialities and I hope I made the point that one must take a total approach.

Dr. Wilcox: Do you have any comments on Langfelder's contention that the thing that is inherited is a sensitive mind rather than disease?

Dr. Rainer: This is the kind of thing I meant when I spoke of psychodynamic description of predisposition to disease. I think sensitive mind is a rather general phrase and we need a more accurate description of what is found in people predisposed to various conditions. I think such descriptions can and should be combined with genetic analysis.

A Theory on the Cause of Psychoneurotic Symptoms Based on Observations of Their Treatment with an Energizer

ROBERT ARNOT, M.D.

A consideration of this problem discloses that there are three sets of theories. One, theories of the cause of the psychoneurotic personality; two, theories of the cause of the decompensation of the psychoneurotic personality into gross psychoneurotic symptoms; and three, theories of the cause of psychoneurotic symptoms.

Before discussing any theory it is well to define our terms. Dorland's *The American Medical Distionary* defines psychoneurosis as a "mental disorder which is of psychogenic origin but presents the essential symptoms of functional nervous disease as hysteria, neurasthenia and psychasthenia." The diagnostic manual of the American Psychiatric Association does not adequately define psychoneurosis, but chiefly presents psychoanalytic theory.

For the purposes of the present paper, we define psychoneurosis as an emotional illness characterized, both psychologically and physiologically, by evidences of excessive tension, anxiety and depression. The psychological manifestations of these three factors are well known: exaggerated self-concern, inferiority feelings, indecision, social anxiety, guilt feelings and obsessive thinking. Physiologically, the same three factors are evidenced in many disturbances of the autonomic nervous system, chiefly those of the sympathetic-adrenal side with palpitation, elevated pulse rate, minor elevation in blood pressure, perspiration, particularly of the hands and feet, flushing of the face, dryness of the mouth, and tension in the stomach. Other physiological symptoms are found more in the voluntary muscles, in the form of tension (as in the nuchal region) and in feelings of fatigue.

We are not, in this paper, speaking of psychoneurosis hysteria. This is a different type of illness altogether, but it has been taken by some to be the paradigm of all psychoneuroses. Hysteria is essentially an avoidance reaction on the psychological level, typically with loss of some function, such as eyesight, speech, sensory powers, or locomotion. This loss of function takes place without any organic change. Theoretically, hysteria could be of psychogenic origin, with psychological changes chiefly, and certainly without the physiological tensions characteristic of the type of neurosis we are investigating. The reason for discussing theories of the origin of the psychoneuroses, at this time, is that the effective use of recently-developed medications has led to new insights into the nature and, perhaps, the true origins of the psychoneuroses.

The particular subject of this paper is iproniazid which has been observed to have beneficial effects on the chronic neurotics with tension, anxiety and depression. From consideration of the effects which this energizer has, it is possible to develop an hypothesis, to explain what is happening in the psychoneurotic illnesses. The patients who respond best to iproniazid might be considered decompensated psychoneurotics, since they are no longer able to perform in the manner, or at the level, that had been useful to them before their illness. Their psychological demands are beyond their physiological powers of fulfillment.

The action of iproniazid in these cases is significant. After one to three weeks of medication, the patients find that they have sufficient energy to carry out their daily tasks and, as a result, they once again enjoy living. The symptoms of anxiety, tension and depression disappear. The medication has helped by affecting their energy output which leads to the hypothesis that a deficiency of energy output is involved in the etiology of psychoneuroses of this type.

In brief, then, our theory is that in the chronic psychoneurotic with anxiety, tension and depression, there is a relative deficiency of energy output in relation to the psychological demands. The sympathetic-adrenal system then over-reacts in an attempt to make up this energy deficiency and in so doing, produces the many familiar manifesta-

tions of sympathetic-adrenal over-activity. Since we have observed that the energy deficiency is relative to the psychological demand, this theory points to a two-fold approach to the treatment of the neurosis. The illness could be treated by decreasing the psychological demands or by increasing the physiological output of energy.

Before giving illustrations and evidence for this hypothesis it might be well to set the theory in its historical perspective through a brief consideration of previous theories on the cause of the psychoneuroses.

An interesting discussion is that by Pierre Janet, who made a distinction between two groups: hysteria and psychasthenia. The phenomena which he called psychasthenia would include the type of psychoneuroses which we are considering. In this group he includes obsessions and compulsions, fears of all kinds, and feelings of fatigue. Janet's thinking was, in part, close to our theory. He believed that psychasthenic illnesses could be produced by a lowering of "nervous tension," or "psychological force, associated with puberty, disease, fatigue or emotion." He spoke of higher and lower functions and believed that, in these states, the higher functions could no longer be achieved. However, he regarded neurasthenia as a long-lasting feeling of fatigue, without physical basis. We would agree with his observation, but not with his conclusion, since we believe that the fatigue does have a real physical basis.

Freud had largely a psychogenic theory of the psychoneuroses, but he also recognized that in neurasthenia, where fatigue was the most prominent symptom, and in the anxiety neuroses, a physical etiology was at work. He conceded that no psychic conflict was necessary to produce the symptoms. Even in illnesses not of purely psychogenic origin, however, he continued to hold a sexual theory of origin. He believed that the cause of the neurasthenia was related to excessive sexual activity and that the cause of the anxiety neurosis was related to sexual stimulation with inadequate satisfaction.

Dejerine was close to the present theory when he said, "We lay it down as a general rule, without exception, that there is always an emotional cause in the genesis of the psychopathic state." Dejerine believed that hysteria developed only where there was "a peculiar emotional constitution."

Ross applied Pavlov's concept and thought that there was a conditioned reflex response in which the patient's reaction was due to previous conditioning to a particular stimulus.

Finally, we find that Weir Mitchell also spoke in a sense close to the present theory, since he regarded the psychoneuroses as due to fatigue, which led him to prescribe rest as the treatment. (*A Textbook of Psychiatry*, New York, Oxford University Press.)

I am indebted to Henderson and Gillespie for this brief summary of the various theories on the cause of the psychoneuroses. They are stated here chiefly because they do point out that, for a long time, researchers have recognized fatigue or asthenia as a prominent manifestation of these illnesses.

We shall consider some case material upon which the present hypothesis is based. Recently, practicing psychiatrists have had very favorable results with the use of iproniazid (Marsilid), in patients with tension, anxiety and depression in many of whom the classical diagnosis would be chronic anxiety. Previously the patient may have been under treatment for many years, and have had courses of electric shock treatment with temporary improvement. With iproniazid therapy improvement is striking. The patient, himself, emphasizes the increased energy output and the new ability to accomplish what he thinks he ought to. He no longer has the feelings of anxiety that plagued him while his energy output was at a low level.

The following case material will illustrate some of these points:

A 28-year-old mother of three suffered from chronic anxiety for four years and was constantly distressed by feelings of inadequacy in caring for the children. She had been trained as a physical education teacher and had hoped that she might be an ideal mother. (Perfectionism is a prominent psychological trait in all of the patients whom I have treated for this type of psychoneurosis.)

At the beginning of treatment, this woman had guilt feelings about her relationship to the children, particularly about hostility between herself and the oldest boy. But when she had been younger, she had had feelings of inadequacy because of her appearance. "I was always fat," she said, and "I never

thought I was very attractive." During her years of growing up, she had also lived in a disturbed family environment. Her father was alcoholic and her mother, like the patient herself, was of a "nervous temperament."

When the patient married another school teacher, she also had a very high ideal of the way in which her housework should be done: "It upsets me not to have the house just so." And, through the long period of fatigue and anxiety she had not been able to keep the house in the manner that she wished.

She showed many other traits of the psychoneurotic personality. She was never able to assert herself sufficiently and frequently she felt inadequate in social situations because of not knowing what to say. Even in driving a car, she did not feel safe, because she was not "fast enough on the gas," or "on the brake." She said of herself, "I am just generally inadequate," and added, "I am afraid most of the time. . . . Everything seems insurmountable, even the slightest thing that I do every day."

This patient had previously been treated at different times with Serpasil, 1 mg. twice a day, Thorazine, 25 mg. five times a day, and Miltown, 400 mg. as needed. She had also had Suavitil t.i.d., of which she said, "I take them three times daily, and I really don't notice any difference." Her reaction to Thorazine was, "It relaxes me to such an extent that I feel I couldn't possibly get up in the morning." Also, "My head was pretty foggy." On the Thorazine, she continued to notice the nuchal tension. Throughout her illness, nausea and epigastric distress were prominent features. She noticed inability to relax and a general weakness of the arms and legs. Compazine, 15 mg. morning and night, produced no striking improvement although it did help the nausea somewhat.

These various medications were given for the treatment of the chronic anxiety. Of them all, she said, "It seems as if they all help at first, for a few days," but she added that the help was slight and temporary.

On November 8, 1957, she was started on iproniazid, 25 mgs. t.i.d. and Dexamyl, breakfast, lunch, and 4 p.m. After approximately three weeks, she began to notice some improvement, and a report seven weeks after the start of treatment was, "Since that time (when the Marsilid was beginning to take effect) I have really felt almost like a human being for the first time in five years." She noticed that she was increasingly busy, and that her poise in company improved. She did not "fall apart," as she had previously, when her husband's relatives came to visit. The Dexamyl was discontinued and the Marsilid continued.

She summed up her reaction to Marsilid as follows: "This has made, I think, a great improvement. I am not scared stiff over anything. Without that great fear, I can handle situations." She gained a few pounds. There was slight dizziness when she got out of bed in the morning, and some constipuation, but she kept emphasizing that she felt "better than I have in years."

At the end of the three and a half months on Marsilid, continuing at 75 mg. a day, she said, "I have been feeling better. It takes away that constant nagging fear, and that deep anxiety that I previously had all the time." By that time her weight had increased fifteen pounds, and although being heavy had been a psychological problem for her when she was young, she did not mind it at all at the present time. As a matter of fact, she was essentially a good-looking woman whose appearance was improved after she gained weight.

At this time, because of newspaper reports of serious liver damage, the medication with Marsilid was stopped temporarily. She returned after she had been off Marsilid for one month, and said, "I don't feel very well." She went back to complaining about her four-year-old boy, who had been one of her biggest problems. She called him "mean and hateful," and said that he had been "absolutely miserable since the day I walked through the door with the second child."

The serum transaminase test for possible liver damage was normal and Marsilid was resumed. In three weeks she was better again. "It takes weeks and weeks before that fear and the nausea and tension wear off," she remarked at our next appointment. She found that, although she was "exhausted" during the illness, she was now able to do her work both inside and outside of the home with real enthusiasm. She describes Marsilid as "the only thing that has helped me in all those years." She is presently on a sustaining dosage of 75 mg. a day. This patient is cited in some detail because she gives a typical picture of the kind of chronic psychoneurosis that is helped with this medication.

Another Marsilid patient, a 28-year-old graduate student who had great difficulty in facing his examinations for his master's degree, and who had spent many years only partially effective due to chronic anxiety, had this to say: "I have never felt better in my life. I sit down at my desk, and for the first time in years, I seem to be learning something. This has made a great improvement." This patient had never been given electric shock treatment, but he had had intermittent psychotherapy, and he had been on numerous tranquilizers without any real benefit.

In another case, that of a 25-year-old secretary, we saw that, as the Marsilid raised the level of energy output and produced a general state of well-being, the patient handled her psychological problems more effectively. This young woman had chronic psychoneurotic symptoms. She complained of fatigue, nausea, and pains in the epigastrium. "If anything happened I'd get a pain. Even going to the dentist I'd have a stomach ache, or coming over here."

Her anxiety feelings made it difficult for her to go to church: "I hated being there." "I hated everything." "I'd come home sick, every time. Always a stomach ache, always shaking, sleepy, dopey, tired."

Marsilid improved her condition, much more, she said, than electric shock treatment. Again this medication was discontinued because of concern on my part about possible liver damage. But as the patient became more desperate with her symptoms and wanted only to die, she was returned to Marsilid, 75 mg. a day. Three weeks later, she reported, "I just started to feel wonderful. I think I feel better than I ever felt. The nausea and pains were gone. For the first Sunday in months, she had been able to sit in church without "hating" it.

"I have a lot more energy," she said. She described working all day, "and then I came home and did his washing (for a 2-year-old nephew) and my washing, and I loved it." "At work it's wonderful. I'm not pushing myself all the time. And I'm doing the same amount of work. Maybe I'm even doing more, but it seems much easier."

She has to serve at a tea, an activity which she had dreaded before; but now she feels that she can serve the next tea easily. "If I could only feel like this, I wouldn't be afraid to go any place because I'd know I wouldn't get sick there."

She had despised her over-strict father for years, but while she was taking Marsilid, she had an argument with him and found that she could speak her mind without becoming upset and without marked feelings of guilt afterward. On the other hand, she said that for the first time she was able to admit that she really felt guilt about things she had done in the past. She felt the guilt, accepted it, and was not tortured by it.

The results in the cases discussed above, where iproniazid helped patients with chronic psychoneuroses, characterized by tension, anxiety and depression, suggest that, in a psychoneurosis of this neurasthenic or psychasthenic type, there is a relative deficiency of energy output. Certainly these patients discovered that on medication with iproniazid they were able to work in a way that was impossible for them before, and since they were able to do this work, they no longer suffered from as strong feelings of guilt and inadequacy.

Would it be possible to say that even in the patients with social anxiety, who feel unable to express themselves, or even participate, in a group situation, and therefore feel inadequate and left out, there is a similar deficiency of energy output? If social anxiety is based on the existence of an actual energy output lower than that of other members of the group, the feeling of inferiority is based on a real situation—one, however, which may be subject to correction through appropriate therapy.

A number of anxiety symptoms may be a by-product of the relative deficiency of general body energy output. As the body attempts to correct the deficiency by an increase of sympathetic-adrenal activity such over-activity produces the various physical symptoms, such as flushing of the face, palpitation, gastric tension, and perspiration of hands and feet, which are common in cases of this type.

We know that in all such cases, the problem combines elements of psychology and physiology. The patient has set for himself an ideal which he cannot attain at his present energy-output level. This leaves him striving for something that he cannot quite reach. Since the illness combines psychological and physiological elements, its ideal treatment should also combine the appropriate techniques from the two fields.

We might say, on the one hand, that the deficiency of energy is relative, since the ideals have been set too high, and we know that the neurotic can be improved if these ideals are lowered through psychotherapy. On the other hand, there is the possibility that the ideals can be attained, or at least approximated, in many cases, with the aid of an energizer such as iproniazid. Also, the energizer frequently gives the patient the additional strength needed to face and solve his purely psychological problems.

This theory would also explain the beneficial effects of EST which have been observed in these chronic psychoneurotics because the EST by effecting the cortex suspends, at least temporarily, the psychological demands, and by effecting the diencephalon acts also as an energizer.

Finally, iproniazid strikes more directly at the psychoneurotic symptoms than do meprobamate, the barbiturates, and the promazines which attempt to reduce the symptoms of sympathetic over-activity without getting at the cause.

Clarification of the Action of Successful Treatment in the Depressions

ANTHONY SAINZ, M.D.

Six years ago, in a well-balanced presentation, Bellak[1] was of the opinion that "manic-depressive and allied disorders . . . were a number of syndromes of multiple etiologies." The data accumulated since his book made its appearance has failed to prove him wrong; although, in general, subsequent publications have tended to group "depressions" as a single disease entity. The general trend, in which both psychodynamicists and organicists have partaken, has stressed the attempted demonstration of the "psychogenic" or "organic" etiologies of this supposed condition, with few if any attempts made to clearly delimit the composition or essence of the disease itself. A notable exception was the recent work of Lehman[2] who re-emphasized that, at least clinically, depression is merely a generic name which encompasses a number of probably independent syndromes.

Since conclusive evidence to the contrary is lacking, it is reasonable to assume that there are various kinds of depressions, and that there may be at least one distinct etiology for each. In spite of the known fact that "depressions" are the psychiatric conditions which most readily and consistently respond to somatic therapy (e.g.: ECT), practitioners of the psychodynamic persuasions have always raised the objection that such drastic physical treatments act, not because of any physical or biological change, but because their traumatic application symbolizes the fulfillment of an unconscious need on the part of the patient.

Thus, it would not be the electrical current passing through the cerebrum in electrocoma, and its biological effects, that would be effective in relieving a depression. It would be the punishment that it represents and for which the patient, smothered in guilt, yearns that would restore tortured constellations to anodyne gestalts, freeing the ego from such agonizing loads.

Nor would severing with a leucotome the projection fibers of areas 9, 10 and 46 of the frontal regions of the brain have any physical import except—to the psychodynamicists—to cause a needless punitive trauma to the "intelligence areas." No, the, leucotome long, rounded, sharp and of virile steel, could well represent an apotheosic phallus, deeply thrust into the very entrails of the brain, satisfying all basic homosexual urges of the patient in a veritable explosion of libido.

That sub-coma ECT is ineffective, albeit more torturesome, and that incomplete leucotomies are equally non-therapeutic raises some doubt regarding the validity of psychodynamic formulations. Then again, why should the symbolic contact with a leukotome relieve a depressed homosexual, when his encounters with real life flesh-and-blood organs gratify, but fail to relieve his symptoms? It is possible that reality is the wrong way of access to the id.

It appeared that to clarify the physical or symbolic effect of the action of electrocoma and transorbital leukotomy would be the most obvious and, probably, the most fruitful initial approach to elucidate the general etiology of depressive conditions. Twenty patients were divided into two groups of ten each by selecting each alternate admission. All twenty (eight men and twelve women) suffered from the depressed phase of manic depressive disorders or from "involutional" depressions, all having in common self-depreciatory and accusatory trends. It was intended that ten of these patients would receive electrocoma and ten would receive "mock" electrocoma.

To achieve this aim, advantage was taken of the fact that all ECT treatments at that time were administered after the patient was anesthetized with Sodium Pentothal. The modus operandi was to place a patient in the ECT room, in bed, affix the electrodes and conduct business as usual up to and including the administration of the intravenous barbiturate, but without ECT. All patients received their treatments individually, so that no other patients would be in a position to tell the subjects that they had not received

the full procedure. Treatments and "mock" treatments were conducted on Mondays, Wednesdays and Fridays for one month.

At the end of the test period, nine of the ten patients on ECT had recovered and one was moderately improved. This last patient later became shock-resistant. Of the ten patients on "mock coma" three became decidedly worse, with suicidal ruminations and further thinking and affectual constriction. One improved to the point of almost full remission and the remainder were unchanged. All nine were then placed on real ECT for twelve comas, administered according to the identical procedure used before—only ECT was added—with the explanation that, since they had not improved, they needed more treatment. Seven of these nine patients effected full remission and two, the oldest "involutionals" in the group, were substantially improved although not in full remission. A similar study was made independently by Kocer,[3] who obtained identical results.

The results of the above tests clearly indicate, with ample statistical confidence, that the mode of action of ECT is organic, on the brain itself (directly or indirectly) rather than symbolic. But while the above tests were under way, four very severely depressed patients, of the chronic type, whose depression had not responded to psychotherapy or to ECT, were scheduled for psychosurgery, transorbital leucotomies being selected as the technique of choice.

The operations were usually done under ECT anesthesia, and in these four cases the procedure was carried out up to and including the insertion of the leucotome. However, no sections of fibers were made, the instruments being withdrawn atraumatically. The patient's eyes were covered with cool compresses on awakening—a procedure the patients would expect—and they were kept from inspecting themselves on a mirror for the next eight days. At the end of this time, it was determined their depression was deeper, if anything, and a real leucotomy was then performed on the ninth day. All four patients were free from depressive manifestations three days later, although one relapsed in six weeks and then required a standard open Freeman-Watts leucotomy before permanent relief was obtained. These results would also obviously militate against the "symbolic" psychodynamic mode of action.

When, in later years, we found chemicals capable of reversing depressions, double and triple blind controlled placebo-studies amply demonstrated that the phrenopraxic action of such psychopharmaceuticals was not due to their shape, color, taste, or to the perception and unconscious interpretation of their endogenously felt pharmacologic action. Yet, while the accumulated data serves to buttress the belief that endogenous depressions, and those of the affective variety, are due to biological disorders, there is no denying that other depressive conditions arise from purely psychological factors, with little disturbance of the organic economy.

How, then, to distinguish between the two kinds? A review of our data indicates that psychogenic depressions (e.g.: "reactive," "stress" or "'neurotic") allow the discovery of the precipitating factor, and the mechanics of the mode of onset are reasonably easy to establish in a very high proportion of cases. On the other hand, affective and endogenous depressions seldom, if ever, show a definitive precipitating cause or clear-cut mechanics of onset, except when a stressful situation may serve to trigger an endogenous condition, as could occur, for example, when a manic/depressive is faced with a sudden affective loss.

Since there is no doubt of this borderline group, it behooves the investigator to so construct his research design as to exclude these controversial and hardto- diagnose individuals from test situations. We have done so in the data here presented.

Experimental and observational data supports the division of depressions into psychogenic, on the one hand, and affective and endogenous, on the other. While orthodox psychoanalysis and the newer intensive dynamic therapies are highly effective in the former, their benefit is highly questionable in the latter—to the point that a careful study will show the same rate of improvement for psychotherapeutically treated endogenous depressions as for their spontaneous remissions.

Conversely, the literature abounds in the spectacular lack of success of the "drastic"

therapies—ECT and psychosurgery—in the psychogenic depressions. We ourselves are in a position to state that a comparable lack of success attends the use of phrenopraxic drugs in these reactions. Yet, ECT, psychosurgery and the phrenopraxic anti-depressant drugs are highly effective in manics-depressed, and in the endogenous depressions.

It is important, at this point, to pencil in the difference that exists between the affective and endogenous depressions, and those depressions that occur in individuals suffering from an organic disease of the brain. We wish to emphasize this difference because we feel that the processes of biological dysfunction which culminate in the described depressions is specific for each, and is not merely *any* organic derangement. Depressions attending organic disease may well be, and we find many that are so, psychogenic, resulting from the intraperception of the subject's disturbed or pathological body-image. They may also be physiological depressions or obtundations based on extensive cerebral damage—all "downesses" are not depressions—and they may be true endogenous depressions triggered by the hegemonial disease. The results of different treatments in patients suffering from organic diseases, who are also depressed, highly compare to the results we expounded above for psychogenic and other depressions, showing that a diseased person may have either type.

Having thus produced data to support our concepts of basic depressive etiologies, it remains for us to discuss—after a brief description of each type of depression we individuate—by what means do the successful treatments operate, to yield a further clue towards the elucidation of the complex mechanisms of depression.

While we agree with Bellak[1] that "the definitive definition of . . . (the affective) . . . manic-depressive syndrome is yet to be achieved," the operational description established by us shows that the characteristics required, as a minimum, for inclusion into an investigative or evaluational group of this type of depression, include a majority of clear-cut cases, weeds out the borderline diagnoses, and in general compares well to the American Psychiatric Association description of parameters. The same can be said for the endogenous depression groups as we delimit (not define) them. This description of minimum essential objective symptomatology is contained in another paper,[4] to which the reader is referred. All observations made in this paper will thus refer to patients manifesting this essential objective syndromology.

When an electric current is applied to the cerebrum, it would appear that the effect would be one of stimulation, particularly in depressions where the paucity of psychic productivity and the psychomotor retardation are often striking. Yet the most "stimulating" currents, those that do not lead to unconsciousness, or "sub-coma" ECT, is seldom therapeutic, although they produce increases in blood pressure, cerebral serotonin and adrenalin, and various corticosteroids. Deep electrocoma, leading to the most complete—even if transitory—unconsciousness, while producing in no greater amount than sub-coma treatments the accompanying physiological changes, nevertheless reverse the depressive state in most cases. It should be taken, then, that ECT may operate by the inhibition of an abnormally stimulated cerebral mechanism, whose exacerbation exerts, de proprio, an inhibitory action on higher cerebral associative and conative thinking centers.

If we compare the action of drugs, for example the combination of mepazine-ethopropazine,[5] methonalide,[6] or, more recently, iproniazid and phenelzine,[7] to that of ECT, it will be easy to revert to the original theory of "stimulation" because the inhibitory effect of these drugs is difficult to appreciate, thus only the excitatory action remains prominent. Further, overdoses of some of these compounds, principally iproniazid, may produce excitements and agitations, which appear as pseudo-manic states. Probably thus was the concept of "psychic-energization" born.

It is our belief that in the categories of depression described the psychopathological picture is produced by inhibition of associative and conative cerebral centers by the exacerbated activity of related structures. Our data also shows that very prolonged or very severe situations of this kind result in the profound and sometimes irreversible

inhibition of motivation, which through our experience we must view as a psychophysiological primary function channeled, or modified, by learning and ecological determinants. The reasons for such beliefs are obtained from the failures of unsuccessful treatments, in these conditions.

We have already stated the whys and wherefores of our belief that electrocoma inhibits—or better yet, reduces to a normal level of operation—certain exacerbated psychocerebral centers. The action of leucotomy appears to be corroborative of this impression, as its action, eliminatory in nature, can hardly be construed as "stimulation"—in a logical way—unless we postulate that this "stimulation" would be relative, that is, the result of a braking or inhibitory effect on a cerebral inhibitory center. Thus leucotomy would actually free from oppression such cerebral structures as were inhibited.

It is as well that we state, now, that the author is unable to locate, from this data, which cerebral areas may be the inhibitor and the inhibited. The fibers sectioned by a transorbital leucotomy, for example, originate both in the cortex and in the thalamus, and there is no way of telling, at present, how many other projection pathways may be involved. The results of the operation leave us no clue as to which center or cellular complex was "liberated." Festinated imputation of specific activity to certain anatomical complexes of the brain, like the cortex, thalamus and the recently very popular hypothalamus, on the basis of present-day anatomical, psychological, physiological and biochemical data, are only hypothetical matters of opinion—an unscientific attitude—and more apt to confuse the issue.

The action of phrenopraxic drugs on depressions shows, in all cases that are successful, an initial "sedative" effect of variable duration. During this phase, more obviously seen with iproniazid and phenelzine than other drugs, a marked feeling of lassitude and well-being is expressed by the patient, who tends to be drowsy and lackadaisical. During this period associative processes increase, but the individual lacks drive and motivation. They show no guilt or concern over this lack of drive and drowsiness, which we have determined is not due to hypotension or hypnagogic effect of the drugs. This is considered to be the result of elimination of excessive overactivity of the cerebral inhibitory centers, which action permits associative and conative areas to return to their normal level of action. This "disinhibitory" phase is followed by return of motivation, normal affect and remission of symptomatology, a process that can be seen occurs in progressively incremented degrees.

In certain depressions ill too long or too severely, the disinhibitory phase is followed by normal affect and remission of symptoms, but motivation does not return. The individual is thus presented as compliant, affectively normal but purposeless. We interpret this to mean that the length or depth of illness has resulted in the loss of a basic psychocerebral function (we prefer this term to "drive," to avoid confusion with this latter term's psychoanalytic connotations) due to the sustained or severe inhibition. The action of three different kinds of drugs allows us to identify a triad of psychocerebral functions which is important in evaluating and appreciating all these conditions.

We shall illustrate by describing the result of different "type" drugs in the same category of depressions, that of the overt endogenous variety. To such a patient, if we administer iproniazid or phenelzine, and this patient has been ill too long and too severely, we will bring the benefits of normal affect and freedom from depression, but not motivation, as described above. If we administer an analeptic stimulant such as metrazol or amphetamine, we will produce only an increased medullo-muscular increase in activity, resulting in agitation and, in sufficiently high doses, even spasms and convulsions, but no relief from the basic affective condition of depression. This may be restated as that we transform, by this means, a coarctated depressive into an agitated depressive (only psychogenic and very borderline cases seem to benefit from amphetamines and other analeptics according to our strictly controlled studies). If cocaine or koladeine are administered, depression may or may not disappear, but motivation and ambition, and particularly the capacity to concentrate and sustain effort, are

greatly incremented, although mood does not seem greatly changed.

Thus we see that each type drug produces a pretty individual result in the same category of patient; selective effects on medullo-muscular activity (analeptics), on affect ("psychic energizers" or psychagogues such as phenelzine), and on motivation (coca and kola). The process of reversing depression is a complex one, and not merely a matter of "stimulation"—as the analytically inclined naively believe—nor of motivation.

In clarifying thus the results of drug and drastic therapy actions on depressions—as defined—it becomes inescapable to conclude that the syndromes involved appear to have a basic biological substrate, much more complex than appears at first glance. We therefore conclude that the syndromes described are biological in nature (but psychologically modified or colored), that their response to treatment is indeed a biological one and not a result of symbolic apperceptions or gratifications, and that the process involves three separate areas; the affective, the motor and the motivational, all of which are simultaneously involved in any depressive phenomenum albeit to different degrees, depending on the length and depth of illness. Successful therapy acts by lowering to normal exacerbated psychocerebral centers whose overactivity inhibits associative and conative, in addition to affective, areas. Electrocoma, psychosurgery and the phrenopraxic anti-depressant drugs act on one or two of the inhibited areas, but only indirectly on all three. The treatment that will simultaneously reach conation, affect and motor areas remain to be produced, but it is hoped the facts presented herein may facilitate research in this direction.

Summary

Taking into consideration only such types of depression as called by the author affective and endogenous, a research design was established to determine if organic drastic therapy beneficially influenced such conditions by their symbolic apperception or through biological action. "Mock" ECT and transorbital leucotomies were compared in results to real surgery and electrocoma applications, under strictly controlled conditions, and the results showed no effect from the "mock" treatments and excellent results from the actual ones.

The action of ECT, psychosurgery and the phrenopraxic drugs was studied and it was concluded that they act by lowering to normal exacerbated psychocerebral centers whose overactivity inhibits associative and conative, in addition to affective, areas, thus inducing depression.

An analysis of the results obtained with all the above methods of treatment, their mutual comparison, and their further comparison with the results obtained with analeptic and special central stimulants of the coca type, brought out the fact that three elements are involved in depressions of the types described; affective and conative inhibition, motivational inhibition and psychomotor inhibition. All the successful anti-depressant treatments studied act on one or two of the inhibited areas, but not all three except indirectly. The complete anti-depressant has not yet been produced.

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The Cerebral Hemispheres, the Unadapted State and Schizophrenia

LORING F. CHAPMAN, PH.D.

In the search for a logic of disease it has often been useful to see disease as the outcome of goal-directed attempts at adaptation which somehow have gone awry, such attempts being either too great, too little, or inappropriate to deal with the conditions which evoke the response. For instance, Claude Bernard saw disease as the outcome of adaptive responses that are inappropriate in degree. The fluid accumulation in pneumonia is an example of such an inappropriate adaptive response.

More recently, we have come to realize that adaptive responses may be inappropriate in kind, as well as in degree. An example of this would be the person with peptic ulcer who responds inappropriately to threat by evoking an eating pattern. Since this eating pattern is unsuccessful in dealing with the threat, it is called forth again and again, leading ultimately to tissue damage. Studies from the New York Hospital[1] have demonstrated that many of the body's organs become more readily damaged during periods perceived as threatening. During such periods vasodilatation, oedema, diapedesis, hemorrhage, erosion, increased friability of tissue, lowered pain threshold, and impaired organ function have been observed in the skin nose, airways, stomach, colon, bladder, vagina, and in the subcutaneous tissue of the scalp. Similar changes often could be induced by appropriate alteration of the environment, as by interviews which augmented or decreased the perception of threat.

The present investigations[2-5] posed the question of whether the brain shares in these damaging effects of prolonged threat, and inquired whether such damage is relevant to those diseases in which the brain is ostensibly intact but in which there are prolonged disturbances of mood, thought, and behavior. We started with a study of patients who we knew had had tissue removed from the cerebral hemispheres. We selected from the files of the New York Hospital over the last 15 years those patients who had had optimal results from their neurosurgical procedures and did not have ongoing disease processes as far as we knew. They were patients either with arterio-venous anomalies that had been excised successfully or people with slow growing neoplasms which appeared to have been removed completely.

We found that with increasing mass of tissue loss there was progressively greater impairment of function, both in the laboratory tests and on the scoring procedures that we developed for rating impairment as seen in daily life.

On the basis of these studies we have had to broaden our notion of the highest integrative functions. Those elements encompassed in the traditional concept of "dementia" or "organic brain syndrome" were not seen unless there was relatively massive tissue destruction. On the other hand predictable defects in the capacities of those with smaller loss were observed. These "small lesion" defects involved the expression of needs, drives, motives, purposes and goal-directed activity, and the ability to maintain proper organization during stress. Anxiety tolerance and frustration tolerance were lowered in these subjects and there was a lowered capacity to maintain or achieve effective and well modulated defensive reactions.

In those with up to 60-90 gram tissue loss the defensive reactions were altered in the direction of being more conspicuous, more frequently than they were attenuated. The same general pattern of defenses exhibited premorbidly persisted. Anxiety, if present before injury, was augmented in those with small lesions. On the other hand, with

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From the Study Program in Human Health and the Ecology of Man, and the Departments of Medicine (Neurology) and Psychiatry, The New York Hospital, Cornell Medical Center, New York, N. Y.

The author, for this paper, was awarded, jointly with others, the R. Thornton Wilson annual award for his contribution to psychiatric research and treatment.

greater than 100 gram loss, these trends were reversed. The defensive reactions in general were attenuated, although they became so "splintered" and poorly modulated that they sometimes resulted in episodes of extremely deviant behavior. Anxiety if present premorbidly also was diminished.

We then applied these methods that had been developed through the study of those with known cerebral hemispheres loss to a group who ostensibly were intact but who had undergone long periods of poor adaptation with prominent and severe anxiety and depression and other evidence of prolonged life stress. The first of these subjects had presented themselves to the outpatient service of the New York Hospital with complaints of severe anxiety and had been diagnosed as having "chronic anxiety reactions." When we applied the measures that had been developed with the brain lesion group to these subjects we found that they were impaired in all of the categories of function that had been found to be predictably impaired in those with up to 150 gram tissue loss. The mean scores of the group matched most closely those with from 60 to 90 gram tissue loss. However, those with anxiety exhibited features not predictably observed in the brain lesion group which would usually enable distinguishing one from the other. These distinguishing features had to do with such things as prolonged histories of inadequate adaptation, interpersonal difficulties, and mood disturbances.

We then studied a group of people with ulcerative colitis, peptic ulcer or frequent and severe vascular headache. Some of these seemed to be at least partly compensated in their overall adjustment. They were still working. They had not had prolonged disturbances of mood, thought or behavior. These compensated subjects showed relatively little impairment as measured. The impairment observed was limited to such defects as lack of adaptive plasticity, the presence of irritability, and ready fatigue. However, other subjects were decompensated. They had severe disturbances of mood, thought and behavior and were not able to carry out their usual patterns of life. The degree of impairment observed in these decompensated subjects was similar to that observed in the "chronic anxiety reaction" group and approximated that seen with 90 to 120 gram loss of tissue from the cerebral hemispheres.

We then studied a selected group diagnosed as chronic schizophrenia. All were in-patients. They had had the same amount of schooling and were cooperative. All were ambulatory and none presented evidence of dietary insufficiency. They were not receiving tranquilizing agents and had not had extensive shock treatment. Their performance on the procedures for assaying highest integrative functions indicated that they exhibited to various degrees all of the limitations in highest integrative functions that followed the loss of up to 150 grams of tissue from the cerebral hemispheres. The average scores of 25 schizophrenic subjects approximated the average scores of those with 90-120 gram tissue loss.

Subjects with prolonged adaptive difficulties and severe anxiety, as well as many of those with schizophrenia, have been referred to as being in the "unadapted state," a term employed to refer to the totality of reaction (physiological, behavioral, and attitudinal) present in subjects who for long periods have perceived themselves to be severely or overwhelmingly threatened and have been unable to achieve adequate over-all adaptation.

Studies of possible mechanisms by which the observed impairment occurs are in progress.[6,7,8] It was observed that the cerebrospinal fluid of hospitalized patients with schizophrenia contains an abnormal amount of a proteolytic enzyme that was found to be elevated also in patients with active inflammatory and degenerative diseases of the central nervous system and in those in whom a prolonged state of excitation within the central nervous system could be inferred. These observations suggest that a significant yet perhaps reversible alteration in metabolism occurs in the brain of patients with schizophrenia. Whether primary or secondary, the observed accumulation of protease, and of polypeptides formed by the action of the protease, could contribute to impairment of the functions of the brain.

This program of study is an ongoing attempt to re-assess the place of psychoses

within a general theory of disease. The broad formulation that serves as the orientation includes the observation that hospitalized patients with chronic schizophrenia exhibit a serious impairment of functions of the cerebral hemispheres, an impairment that shares all of the features of impairment found predictably in those with major tissue loss from the cerebral hemispheres, but colored and overlayed with the special features which make possible their ready differentiation in most instances. It is possible that in some patients with schizophrenia the impaired function is the result of a series of faulty adaptive arrangements elaborated during prolonged exposure to circumstances perceived as threatening and involving either the brain itself or other bodily organs. The absence of histologically demonstrable structural changes in the brain of patients with schizophrenia suggests that the defect may be at the biochemical level.

Each individual exhibits his own degree of over-all adaptive capacity, determined largely by the resolution of many forces acting to establish the functional capacity of the brain; among these are the genetic endowment, embryological development, the state of functioning of the other bodily organs, and to an extent not shared by other organs, proper interaction with the environment—particularly in the early years. Anyone of these may be so disturbed as to be decisive in reducing over-all adaptive capacity, a most fragile feature of the brain's functions. Factors as diverse as genetic errors, prolonged adaptive difficulties in early life, or direct trauma to the brain may have the common result of reducing the capacity to assume adaptive load, making circumstances overwhelmingly threatened for long periods, and some satisfactory level of over-all adaptation is not achieved, the functions of the brain are impaired—at first reversibly and ultimately apparently irreversibly. Our studies of the cerebrospinal fluid indicate that during prolonged stimulation and during other states in which catabolism leads over anabolism within the central nervous system, a proteolytic enzyme is liberated and sometimes bradykinin and serotonin accumulate in the extra-cellular fluid of the brain and in the cerebrospinal fluid. From the many properties of these substances that link them with inflammation it seems likely that treir accumulation interferes with proper neuronal function.

Thus, these studies partake in the ancient hope that some basic feature of the disturbance of those with serious and prolonged disturbances of mood, thought, and behavior in spite of an ostensibly intact nervous system, may be detectable at a chemical level and that appropriate modifications at this level may lessen or remove the impediment for re-education and guidance towards effective interaction with the environment that is characteristic of those with psychoses.

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A Comparative Study of Adolescents with a New Drawing Test of Projective Technique

FERRUCCIO A. DI CORI, M.D.

J. E. D. Esquirol, in France, was the first in the psychiatric field to register interest in the artistic production of mentally defective children. Cesare Lombroso in Italy and Max Simon in France, at the end of the century, became fascinated by the drawings of "insane people." Lombroso, however, defined these drawings as "arabesque," and Simon was shocked at "the licentious expressions" of his inmates. The Freudian concept of "archaic heritage," the Jungian theories of collective unconscious, followed by Paul Schilders's "concept of body image" and Nolan Lewis's studies in art projection can be considered among the basic elements which led to an organized approach to the study of projective techniques.

The graphic expression of a human being drawn at a primitive and uncontrollable level is essentially honest and therefore represents a doorway to a labyrinth which, although filled and interspersed with many pathways, represents a map of relay systems for the psychiatric investigator. Karen Machover expresses this concept clearly: "Personality does not develop in a vacuum but through the movement and feeling and thinking of a specific body: a body in action." The drawing done by an individual represents, in the last analysis, the drawing of a self image. In the same way, an artist takes into account two elements—the subject and himself. On the basis of these concepts I devised a test of projective technique—a drawing completion test—which was introduced last year and which has proved to be a diagnostic as well as a prognostic aid in the study of the personality.

The test is given on a blank sheet of paper on which six boxes of equal size are ruled. (Figure 1.) The first box labeled "Ego" has a dot imprinted in the upper left corner. The second box, "What I would like to do," is completely blank, the third, "Home," has a small rectangular box drawn in the right lower corner. The fourth, "Friendship," has two parallel lines drawn in the upper left and lower right hand corners. The fifth box, "Stability," has a wavy line in the lower half, and the sixth box, "Sex," has two lines in the right lower corner, the outer line slightly longer than the inner one.

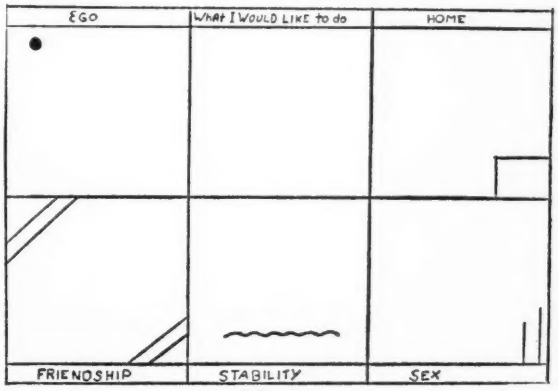


Fig. 1.

The patient is asked whether he understands the titles written in the squares. If necessary, explanation of the captions is given: i.e. "Ego" is yourself; "Stability" is "steadiness, firmness, balance," etc.

The patient is then asked to draw in each box anything he wishes which refers to the titles. Before starting to draw he is told that it is not a drawing test and no artistic ability is required; that "the drawing is completely free," the subject may draw in any style he prefers (abstract, concrete, stylized, etc.); each drawing, however, must include whatever mark is already found in the box; no time limit is set. If resistance or lack of comprehension is encountered, the patient is asked to repeat aloud the instructions, to prove that he understood them.

Rationale of the Test:

The rationale of the test is based on the fact that the patient is confronted with a sequence of six boxes which appear, at first glance, to be practically empty. The upper center box, "What I would like to do," represents at first, a wide empty space into which the patient can express anything he wishes. On either side, the "Ego" on the left, and "Home" on the right, represent

mild stress stimuli which, to a certain extent, should coerce the patient either to express himself openly or to withdraw.

In box No. 1 (Ego) the dot at the upper left is intended to represent an abstract concept of the ego placed as high as possible and still kept within limitations. A similar provocative stimulus is found in box No. 3 where "Home" is either a "Box" in which to seek refuge or a base from which to expand into a more satisfactory concept. In box No. 4 (Friendship) a limitation is established by the double line at the margins of the square: from both sides the meaning is "Help might come if you seek it and it will be given." The concept of "Stability" (Box No. 5) is purposely expressed by a wavy line in which the curve is only slightly accentuated but upsetting enough to produce, at times, a feeling of instability. Sex (Box No. 6) is intended to suggest in the simplest schematic fashion a concept of male and female. Once the test is completed the patient is asked to elaborate and explain the concept expressed by his drawings.

The first pilot study of 150 patients from private office practice comprising 78% psychoneurotic and 22% schizophrenic and schizo-affective disorders yielded many interesting findings. The patient was able to bring to the surface structural elements of his personality, unconscious needs and drives, which he had not revealed either in his ordinary interviews or through other drawing projective techniques. It was then noticed that some of the patterns and symbols expressed in the drawings could be utilized in the formulation of the diagnosis of the patient and, more important, in the understanding of the dynamics underlying the conflict. On the strength of these findings a systematic study of samples of "normal" population was undertaken. The findings form the bases of this communication.

The purpose of the study was to investigate a sector of "normal" adolescent population and to study the inäuence of environmental factors such as home and school based on religious and racial background. Our subjects comprised 150 adolescents (142 boys and 8 girls) consisting of a group of 100 boys from a Brooklyn Catholic parochial school; a group of 25 boys from an orthodox Jewish community in the Bensonhurst section of Brooklyn and a group of 25 (17 boys and 8 girls) selected from a Reform Jewish congregation in Mount Vernon, New York (Figure 2). None of the subjects was known to the author in any manner and the author had only a general idea of their familial and religious background.

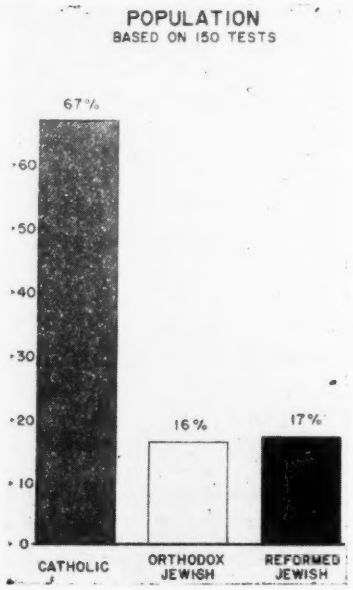


Fig. 2.

The Jewish orthodox community is a close knit, amalgamated clan, where religious ties act upon the individual stimulating a feeling of: "I am duty bound by the order of the leader," be the leader the supreme maker or the representative of the community on earth. The author came in contact with these boys during the Jewish holiday season and watched them interact before, during and after their long hours of prayers; an atmosphere of home versus religious school and vice versa was the setting for their living.

The Mount Vernon congregation is a characteristic type of a reform Jewish congregation attended by a middle class Jewish population, supervised by a rabbi, a psychologist himself, and a member of the Rorschach Institute. The author visited the congregation during their Sunday school hours and the test was administered during classes in the presence of the teacher.

The social milieu of the Catholic school population was represented by a middle class type with some tendency toward the low eco-

nomic status. The test here, was administered by the author in association with one of the teachers, whom he personally trained.

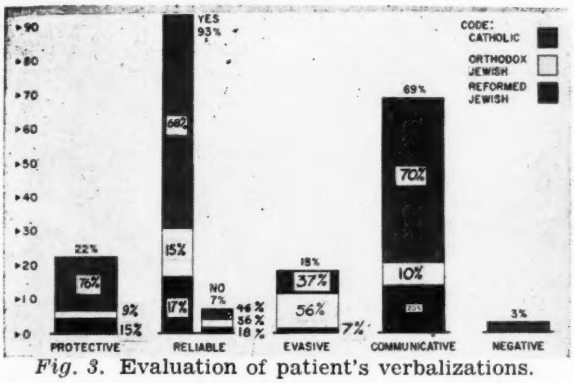


Fig. 3. Evaluation of patient's verbalizations.

The groups cooperated fully in the test, exhibiting interest and often enthusiasm. The adolescents were chosen as a first sample investigation because they represented not only a period of growth in the development of human personality, but also an expression of a period of transition, full of situational stresses; a period in which one is bound to find strong intimations of the struggle between the insurgent, powerful sexual urges and the forbidding moral boundaries of the "Super Ego" (Figure 3). The adolescent no longer indulged in infantile expressions (pleasurable escapes); he yearns to identify himself closer and closer with adult figures (hero worship, etc.), but his psychological structure is not yet sufficiently organized to support the inevitable clashes that occur between the two opposite drives; the Ego strength of the adolescent has not yet developed enough to balance the struggle. On the basis of these premises it was expected, then, that certain patterns of deviation (disturbances) in the field of the unconscious would be revealed through the test inasmuch as important areas such as "Oneself," "Home," "Friendship," "Sex," would be attacked and brought to the surface.

EGO	WHAT I WOULD LIKE TO DO	HOME
PROJECTED RESTRICTED AGGRESSIVE PROTECTIVE	REALITY PHANTASY	DIRECT CONTACT WITH ENVIRONMENT INDIRECT CONTACT WITH ENVIRONMENT REFUGE SECLUSION INDEPENDENCE REJECTION
FRIENDSHIP INDIVIDUAL RECEPTIVE FASSIVE OUTGOING ACTIVE SOCIAL ENVIRONMENTAL SUBSTITUTE DISGUISE	**STABILITY** PERSONAL PROJECTED IN MILIEU SYMBOLIZED	**SEX** SUBLIMATED REPRESSED EXPRESSED OPENLY EXPRESSED IN DISGUISE RATIONALIZED ABSTRACTED SYMBOLIZED

Fig. 4. Method of classification of responses.

The results were as follows:

1. *Ego:*

A. The Ego in 65% was "projected" and in 18% showed some aggressiveness. Only in 21% was there a tendency to withdrawal or defence. Differentiating this one from a previous group of adults tested in the previous research project, where the "Ego" showed timidity, fear, lack of drive, inability to stand the challenge of the stimulus, and most important a tremendous protective defense.

B. Hostility toward the father's figure was repressed or channelled. Instead it was evident an identification with an authority invested figure (teacher, God).

C. Expressed plasticity (adaptability to environmental stresses, trauma, etc.) as revealed by many drawings in which concept of home, stability, sex, showed the ability of adolescent to deal with these concepts less rigidly than the adults.

2. *What I Would Like to Do:*

On the strength of the projected elements drawn in the first area, the second box was, to a certain extent a *consecutio in tempore,* e.g. a projection in the future; "I will be what I dreamed to be if I . . . will be able to make it" seemed to be the feeling born out of this area.

The concept of reality versus phantasy was based on the scattered aspect of the responses, their heterogeneous features, their feasibility projected in the future of the subject's life. The results in percentage showed fantasy 51%, reality 49%. An adolescent almost always dreams and projects in the future: how he dreams and what he dreams of, is the most relevant factor in this sector.

3. *Home:*

The stimulus was as unstructured as possible, but still disturbing enough to represent in the reaction of the individual, a home plate, a center, a springboard. The reaction of the subject was analyzed on the base of his interpretation; both on a verbal and non-verbal level. In this survey "Home" was considered, at times, as a dwelling or as the "abiding place of one's emotions" or as the social unit or the center formed by a family living together. At times, instead, it was interpreted as a refuge, and at others as seclusion (53%). But the area was also expressed as a bridge to gap the abyss of the world at large; be this gap a strong and firm rapport (direct contact of environment: 13%) or a tenuous, fragile, unreliable, tiny passageway (indirect contact with environment, 27%); the heading: independence—rejction showed only 15% of response.

Thus, the entire area could be studied as a plurivalent structure from the point of view of bare-

Method of Classification of the Responses:

For recording purposes, a method of classification, was devised according to:

A. Content of the drawing
- Concrete
  - Detailed productive
  - Limited unproductive
- Abstract
  - Schematic- geometric
  - Surrealistic

B. Type—Symbolism of the drawing

C. Verbalization of patient
- Protective
- Reliable
- Evasive
- Communicative
- Negative

D. Interpretation of the clinician

E. Structural form (lines, perspective, etc.)

ness of responses, which were limited, at times, content of different structural elements (configuration of house, type of dwelling, externalization or internalization of concept) animated personalization (presence of people, projection of oneself in the milieu: "I and my clan; . . . which member of my clan is closest or most important to me," etc.), projection of adolescent's own drawn figure (details of "his" representation in the drawing).

4. *Friendship:*

In this survey, this area is a delicate one to analyze. It expresses, probably the entire dynamics of the personality of the "adolescent" period, inasmuch as this is the chronological and psychological period in which the growing youth attempts to trespass the boundaries of sex and manages, metaphorically speaking, a few commando raids, into the field of his opponents. But the adolescent is not yet confident of his own resources and potentialities and occasionally tends to overfocus his limitations. Normal homosexual strivings are at play and override, quite often, the true strivings, which are repressed although ill concealed. The drawings show the adolescent, at times (25%) outgoing active in search of support, completely identified with his own sex, or receptive passive (15%—strong hand shake, abstract lines, verbalized in terms of "support from friendly neighbors" or universality of concept.) The image also becomes suffused in some samples by an aura of total identification with his own sublimations (such as drawings which express achievement in the sports and intellectual field) or, even more puzzling, it shows a total identification with a racial feeling of inferiority (orthodox Jews drawing the flag of their own country: 42%).

5. *Stability:*

Here the adolescents show more abstraction and subtle shading of understanding than adults previously studied. Projection is shown in most of the cases in abstract style, with less limitation and deeper feeling of approach to the given stimulus. Not only the drawing, but its verbal interpretation, shows an inner need of reassurance, a feeling of a concept of stability which is not part of adolescence except in the youngsters' strivings.

6. *Sex:*

In this area a varied range of expression was given by the adolescents group. The drawing reveals the following proportions: 53% expressed in disguise; 13% repressed; 9% sublimated; 7% expressed in rationalization; 3% expressed openly.

The period of adolescence is represented by increasing instinctual drives and need for gratification. The adolescent is unconsciously aware of the struggle within and tries to balance it either by socially introverting his impulses or by intellectualizing them. Hence the largest percentage of drawings in his area shows sex expressed in disguise (53%) and the other percentages revealing the different mechanisms of defense at work. Sex expressed openly yielded only 3% of responses. (Figure 5.)

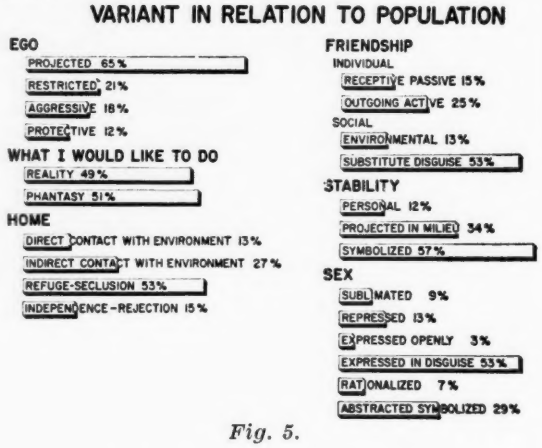
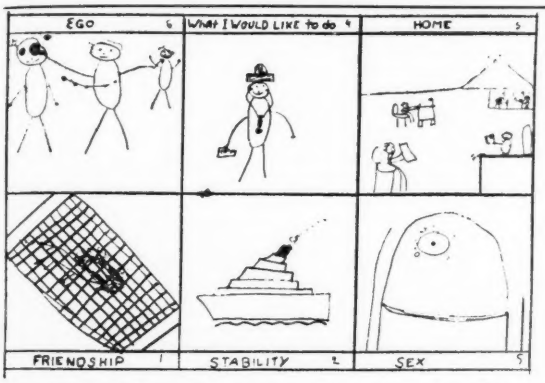


Fig. 5.

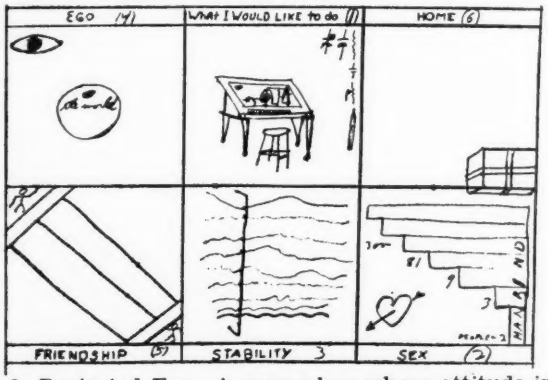
Comments and Conclusions:

This test establishes an easy rapport with the subject, which allows him to express himself non-verbally, projecting the whole of

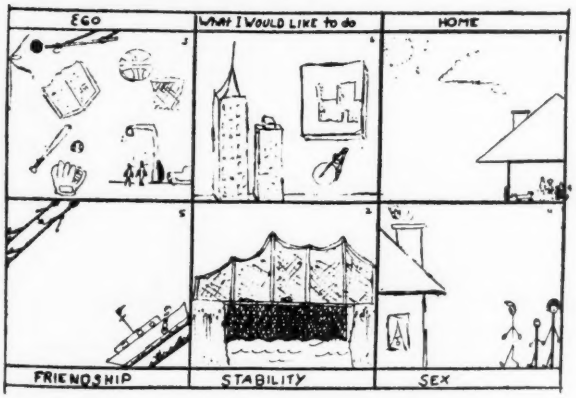
his personality structure in different areas, covering both behavior and feelings. The appraisal of personality being done on verbal and non-verbal levels throws further light on the diagnostic formulation of an adolescent personality by defining "areas of gray shading," such as undisclosed feelings of homosexuality which are revealed in the area of sex or a sense of rejection which although not expressed verbally is uncovered in the drawing of home; or feelings of hostility toward the environment which are projected in the drawings in the area of friendship, etc.



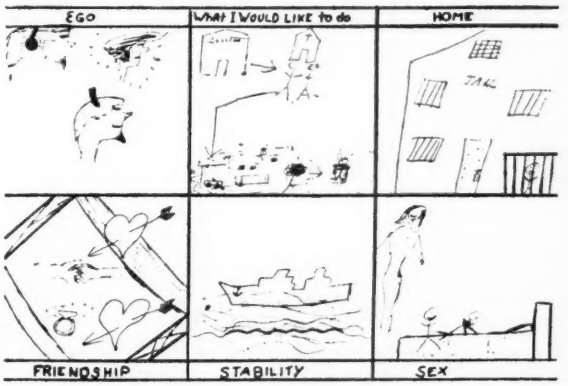
1. Aggressive Ego. A boy with avocational interest in medicine. Basic relationships with friends is mistrust and fear. Shows aggressiveness in the expression of his Ego.



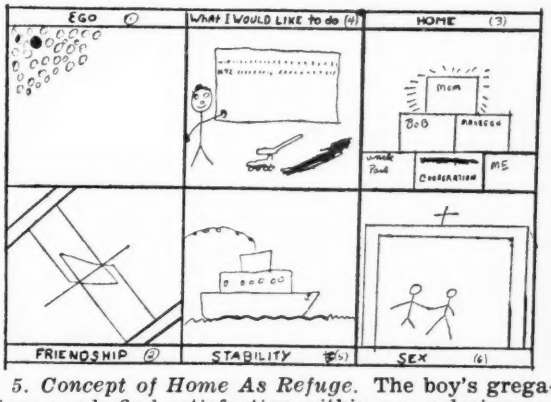
2. Projected Ego. A young boy whose attitude in sex is statistically expressed. His concept of stability is given by physical awareness. Shows feeling of separation and estrangement in the area of friendship and home. His outlook on the world (Ego) is mediate and aloof.



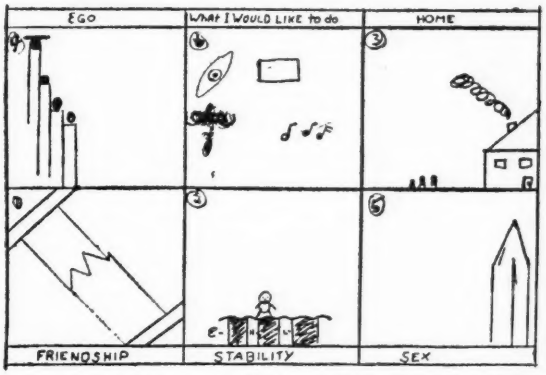
3. Reality in What I Would Like to Do. A boy of varied skills, concrete in aim, optimistic and forceful, whose goal in life is rooted in the practical and ordinary.



4. Concept of Home As Seclusion. A divided concept of self, which is impetuous, but he considers his home a jail preventing enjoyment of friendship and sex.



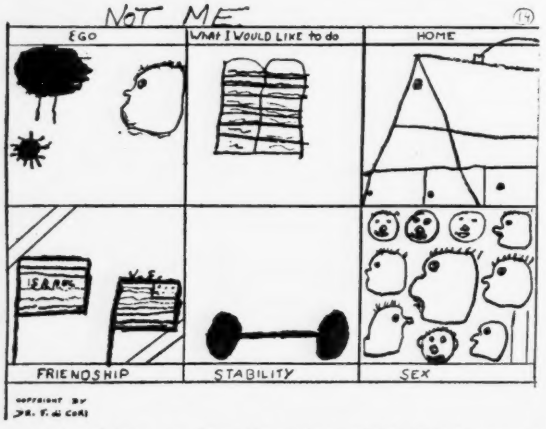
5. Concept of Home As Refuge. The boy's gregarious needs find satisfaction within an enclosing environment. Home area shows him at the bottom of pyramid with "shining mom" on top.



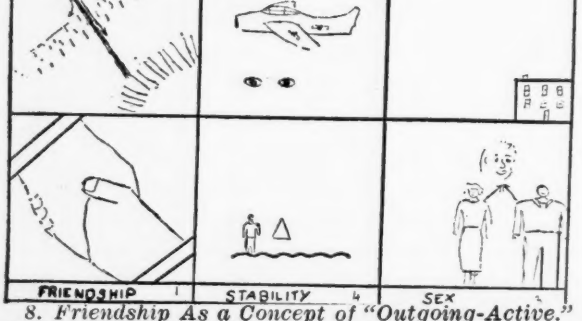
6. Friendship As Substitute Disguised for Sex. In this subject, whose concept of ego is "topping the others," the area of friendship shows an attempted, almost total *"fusion"* fully expressed in the area of sex.

Clinical investigation demonstrates that these areas of shading are the very ones in which the individual finds himself inadequate, disoriented or totally disturbed. As the actual projection mechanism is expressed at a primitive undifferentiated level, then it applies to all regardless of the intellectual achievement or potentialities of the subject. Because of the organization of this test, a trained investigator will be able to elicit not only warning signals of the main breaks but also minute, correlated details that exist between the different areas.

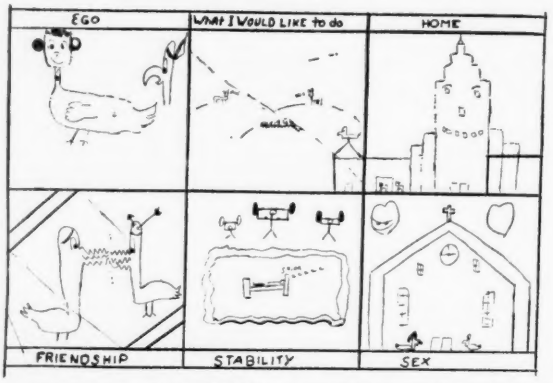
This test differs to a certain extent from other drawing completion tests. Although unstructured and not subjected to cultural restrictions, our test allows one area of the personality to be matched against another, showing after the subject's verbal interpretation, not only the degree of integration of the individual but also the flexibility of his defenses, the sensitivity of his emotions and the maturity of his intellect.



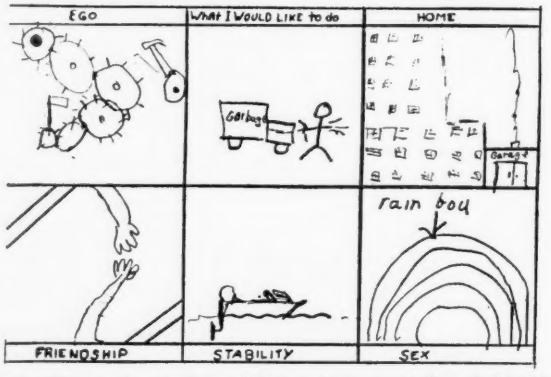
7. Friendship As Identification With Environment (Substitute Disguise). An orthodox Jewish boy, whose compulsive personality shows definite fear and inferiority feelings in the area of friendship and identification with protective authority. His concept of Ego is projected into the area of sex by scission.



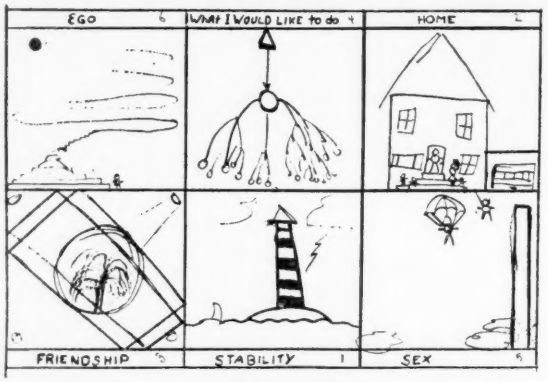
8. Friendship As a Concept of "Outgoing-Active." A personality who wishes to conquer through difficulties, shows social relationship well defined in the area of friendship.



9. Concept of Stability. A definite schizophrenic personality, "Kafka-like," whose concept of stability is expressed in dreams of "barlifting" strength while asleep. His personalized concept of home is populated by animal figures, whose everlasting presence also clouds the entire structure of his personality.



10. Concept of Sex Abstracted and Symbolized. This quizzical character, son of a doctor, finds beauty and harmony in a sublimated area of sex. The discord between his concept of Ego ("This is my brain") and Friendship is more evident when compared with his expression of home and stability.



11. Influence of Religious Theme on Concept of Sex. The religious foundations evidenced in dependence upon God for one's occupation (Box No. 2) and stability finds its clearest statement in sex: "Sex can be good and bad. One jumps off without parachute—(wrong); the other with parachute—right. All depends on circumstances. Sex without marriage (this is the parachute) is wrong.

The adolescent group was selected as the first sample in the large body of the normal population because of its particular challenging ground, showing a tender and yet not well defined personality. At this age powerful instinctual urges clash against inadequate mechanisms of defense—hence conflict and underlying ferment.

The study of the difference in religious background was designed to answer the question: "Does a particular form of indoctrination strengthen or weaken or disturb a certain area of personality?" Religion supports certain mechanisms of defense which the individual tries to gather for himself whenever he feels that a losing battle is being waged within his own inner psychological territory. For instance, in the completion drawing on friendship the subject reveals his sublimation of sex through disguised figures. This gives him subconscious religious protection against the "evil" of sex. Furthermore his intellectualization of sex in the drawing itself represents sex as "harmful" or "forbidden" except in marriage and this is also a concealment of his urges.—In the drawings of home the family represents an island of protection against premature actualization of his instinctual drives, while on the surface this restrictive influence of religious ties may seem repressive, actually these ties set realistic boundaries in which the adolescent feels safer. They are not roadblocks or handicaps, but as religious mores, they may be considered bypass mechanisms which do not necessarily lead to an unwelcome outcome of a situation. The impact of religious influence, in this study, is more evident in the Catholic group

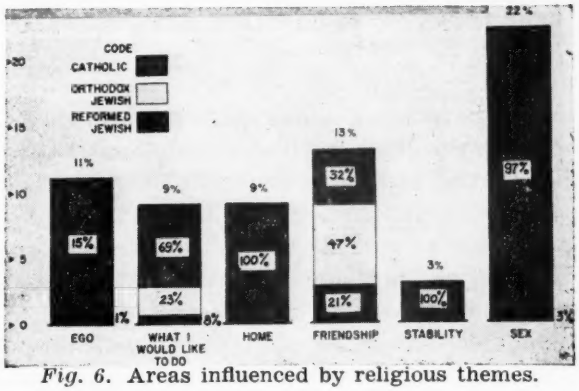


Fig. 6. Areas influenced by religious themes.

than in the Jewish (both orthodox and reformed) (Figure 6).

The clinician deals with unsystematic behavior samples. The purpose of a test is to help the clinician to systematize his material, that is, to bring an objective contribution to his investigation. However, a test is valid, especially in projective technique, when it is considered in its entirety. To attribute too much influence to a minute detail would be tantamount to being antigestaltic and in antithesis with the concept of projective technique.

For this reason the technical psychological knowledge of the examiner and his clinical intuition have to be present and combined in order that a method of exploration such as a drawing test should become the diagnostic tool that would reveal the behavior dynamics and the emotional feelings of the subject. The signicant aspect of a diagnostic investigation lies mainly in the fact that it represents a guiding beam to a therapeutic approach. If a method of approach is objective enough, the therapy that follows will be more fruitful.

Graphic Illustration in Medical Writing

CONRAD M. AYRES, M.D.

The purpose of illustrative material is to lend clarity and interest to the text. The illustrative technique generally used in medical literature, particularly in psychiatric reports, is the graphic method of illustration. Graphic illustration includes tables and graphs or diagrams, collectively referred to as charts. When the medical author is ready to translate his thoughts and findings into words, there is available to him a wealth of written counsel on how to prepare a manuscript; however, information on graphic illustration is rather scarce.

Some of the rules for composing the text of medical writing can be applied to the preparation of illustrative material. Hewitt[1] urges that medical reports be written with objectivity and clarity on timely subjects of actual interest to the audience for whom they are intended; or, as he sums it up, "Thou shalt not write medical papers to please thyself, but to meet the needs of thy readers." As an integral part of the presentation, the illustrative material should be no less clear, no less objective, and, certainly, no less interesting than the text of the paper. A clear graphic presentation refreshes and enlightens the reader and makes the observations and conclusions of the author more acceptable. Charts that are difficult to comprehend are tiresome and confusing. Griffiths[2] stated it very well in a letter to the writer: "The value of charts is in their simplicity and easily comprehended information at a glance."

Jordan and Shepard[3] advise the medical author to set aside his manuscript for a week or two before drafting the final copy. This enables the unconscious mind to assimilate the subject and allows the conscious mind to view the paper with fresh attention and interest. These authors find that the writer who follows this rule never ceases to be astonished by the number of errors he uncovers and by the degree of improvement he can effect. They state that what makes easy reading was often laborious composing and conclude that in some instances the difference between a first-class manuscript and an inferior one is determined by painstaking revision. In this connection, Hewitt[1] states that the natural narcissistic tendency of medical writers to resist correction of their own manuscripts is often even more strongly manifest when they are faced with alteration of their illustrations. Of course, the unending revision of tables and graphs is impractical, time-consuming and expensive, and it definitely reveals lack of preliminary planning and organization.

The medical writer should bear in mind that while the text of his paper is generally subject to competent professional editing prior to the actual printing, the illustrative material is likely to be considered inviolable by professional editors. Visual and logical organization of charts must be undertaken by the author himself and not left to the editors. However, Fishbein[4] recommends that where complex illustrations are concerned, a professional medical illustrator be consulted. The latter with his knowledge and experience of visual techniques, will not only be able to clarify the author's charts but may even be instrumental in carrying the author's intentions a step further.

It may be mentioned here that just as one should avoid excessive verbiage and telegraphic style in the text of a manuscript, so one must aim to achieve a happy medium between profusion and inadequacy in illustrative material. Whenever the information contained in a chart is obtained from another source, it is good policy to mention its origin. This lends authority to the presentation, satisfies ethical considerations, and gives the reader reference for further research. Explanatory phrases pertaining only to a special item or part of a chart are generally shown in footnotes. Samples of symbols for footnotes of charts are shown in Figure 1.

SYMBOLS OF FOOTNOTES GENERALLY USED IN CHARTS ARE THE FOLLOWING IN THIS SEQUENCE:

* † ‡ § ‖ ¶ #

Numerals should not be used as symbols of footnotes in charts lest they be confused with numerical data therein.

When additional symbols are needed double versions of the above may be used.

Fig. 1.

Other general principles to be considered in the preparation of medical illustrations are the following:

1. *Style.* Consistency of style is achieved by uniformity of lettering and labelling in all illustrations of a given paper. Lettering of the title is properly of a larger size than that of caption on a chart; lettering of footnotes should be still smaller.

2. *Readability.* Well-printed charts with careful lettering and large figures, and without superfluous captions and background lines, make for easy reading.

3. *Presentation.* Variety of presentation is obtained by emphasizing significant data with arrows, by reversal from black to white of letters or figures in special parts of a chart on a reversed background, and by the use of more than a single type of diagram.

4. *Layout.* A preliminary sketch should determine the size, appearance, proportion and contrast of the various parts of a chart. A well balanced chart fits into a standard page, can be read without turning the paper sideways, and stands out clearly by the inclusion of suitable margins on all sides. Careful organization of the chart elements will bring out significant trends, comparisons and correlations.

The following sections deal with specific characteristics of tables and diagrams, respectively.

Tables

The statistical table is a systematic arrangement of numerical data in columns and rows for analysis, comparison, correlation and reference. Its purpose is to present data objectively and in a relatively limited space and to facilitate reading and comprehension.

There are two main types of statistical records:

1. The work sheet, general reference table or statistical sheet.
2. The special reference table, table for publication, or statistical table.

The Work Sheet: Every scientist who engages in original research must maintain a work sheet on which he records at full value the results of individual observations gathered throughout the study. The work sheet is, therefore, the source of reference for all the data under study, including both the test patients and the controls.

A clinical study is based primarily on proper samplings of test patients and controls, obtained with selection by the random method as opposed to a biased one. Moreover, the test-patient group should be both homogeneous and large, in order to be considered representative of a given group of individuals and of a given type of illness. The control patients should comprise a corresponding collection of comparable subjects, having the same type of illness. Strict alternation in the choice of test and control patients provides properly matching samples. When possible, the same test patients may be used as their own controls at different times in experimental research.

There may be some justification for using small groups of patients in preliminary investigations, but non-homogeneous sampling and inadequate controls always entail a waste of time and energy disproportionate to the significance of the results obtained.

Since the work sheet is the foundation upon which the ultimate results of the investigation depend, it must contain for each case under observation as much information as required by the scope of the project under study. This information, besides age and sex, may include such elements as civil status, I.Q., genetic type, personality and emotional problems, educational and economic levels; religious, cultural and racial background; type, duration and severity of illness; previous forms of treatment, intensive therapeutic dosage, maintenance dosage, frequency of observation during treatment, and length and frequency of follow-up observation.

The profusion of information necessarily contained in the work sheet makes its reading laborious, if not unintelligible, to anyone except its author. From the work sheet the reader cannot determine what the significant findings of a study are, or even what the data prove or disprove. In other words, the work sheet is a kind of catalogue and therefore lacks the basic requirement for publication of a graphic illustration, namely, to clarify and attract interest to the text. Moreover, the work sheet often contains the

patients' names, their hospital case numbers and other confidential and identifying personal data which should be scrupulously withheld from publication. The work sheet, properly, is the basis for the construction of special reference tables containing the research findings for publication.

Special Reference Table: The table for publication is a logical arrangement of data in columnar form whose purpose is to emphasize specific relationships and to point out special meanings.

NEW YORK ST. DEPT. OF MENTAL HYGIENE — BROOKLYN STATE HOSPITAL - SEPT. 1, 1958 — N. BECKENSTEIN, M.D., DIRECTOR

INPATIENT POPULATION AND M.D.-INPATIENTS RATIO*

INPATIENT SERVICES	PATIENTS						M.D.'s†			M.D.-PTS. RATIO‡		
	TOTAL NO.			PERCENT			M Svc.	F Svc.	M&F Svc.	M Svc.	F Svc.	M&F Svc.
	M	F	T	M	F	T						
INTENSIVE TREATMENT	184	253	437	11%	12%	11%	9	10	19	1:21	1:25	1:23
MED. & SURG. TREATMENT	870	1120	1990	52%	51%	52%	6	7	13	1:145	1:160	1:153
CONTINUOUS TREATMENT	614	790	1404	37%	37%	37%	4	4	8	1:154	1:198	1:176
TOTAL	1668	2163	3831	-	-	-	19	21	40†	1:89	1:103	1:96‡

*DATA OBTAINED BY COURTESY OF DR. NATHAN BECKENSTEIN.
†NOT INCLUDED 6 M.D.'s ATTENDING ALL INPATIENT SERVICES: 1 DIRECTOR, 3 ASS'T DIRECTORS, 1 PATHOLOGIST, 1 SICK-BAY OFFICER.
‡OVERALL M.D.-INPATIENTS RATIO = 1:83 (46:3831).

Fig. 2. A statistical table.

When a manuscript contains more than one table, each one should be numbered. Every table for publication should have a title. The title should be clear, concise and specific and should indicate the subject, place and date to which the data in the table pertain. A proper title gives direct answers to the questions: "What? Where? and When?" and is so composed as to arouse interest in the subject with as few words as possible. To avoid taxing the reader's attention with cumbersome phraseology, a subtitle in smaller lettering may be used.

Besides the title and, when necessary, the number and subtitle of a table, other basic elements in the construction of a table are:

1. Column captions
2. Row captions
3. Numerical data
4. Lines

Column Captions: The space at the top of the table, containing the heading and subheadings, constitutes the boxhead or column captions. Captions should be arranged parallel to the base of the page whenever possible so that the table need not be turned sideways to be read. Perpendicular column headings are laborious to read and should be avoided.

Row Caption: The captions in the entire first column at the left side of a table serve to identify the horizontal rows of figures and constitute the row captions or stub of a table.

Numerical Data: The arrangement of the data makes up the body of the table and should be as clear and uncluttered as possible. Numerical data may be shown directly, as in the work sheet, or with figures derived by calculation, i.e., averages, percentages, logarithms, etc. Data should be so presented as to bring out trends and comparisons, provided consistency is maintained throughout. Totals usually appear in the right column of each table or section of a table and in the bottom row.

Lines: A single line surrounding the entire table is preferable. Double lines are used to separate column captions and row captions from the rest of a table. Heavy vertical lines are used to separate different sections of a table. Thin lines, both horizontal and vertical, serve as a guide to the eye in examining individual data and surveying complete rows or columns of figures.

Tables should always accompany graphs or diagrams whenever the latter are part of illustrative material.

Graphs or Diagrams

Graphs or diagrams are schematic representations of tables and interpret numerical data in visual form for the reader. They save time in analyzing tables, bring out trends, comparisons, and correlations, thus emphasizing the highlights of the findings and delivering information quickly and clearly. The principles for enumeration, titling and subtitling of tables apply to graphs also. Striking visual effect may be obtained by reversal of black and white in the entire area of a graph.

The three main types of graphs or diagrams used in medical writing are:

1. Linear diagram, also referred to as polygonal graph or curve chart (including silhouette chart and scatter diagram).
2. Bar diagram or chart, also referred to as a columnar graph (including histogram and step diagram).
3. Circular diagram, colloquially referred to as a pie chart (a type of area diagram).

Linear Diagram: The linear graph is a rectangular diagram on which varying quantities are expressed by a line, called the diagrammatic line moving across a grid or background ruling, which facilitates visual evaluation.

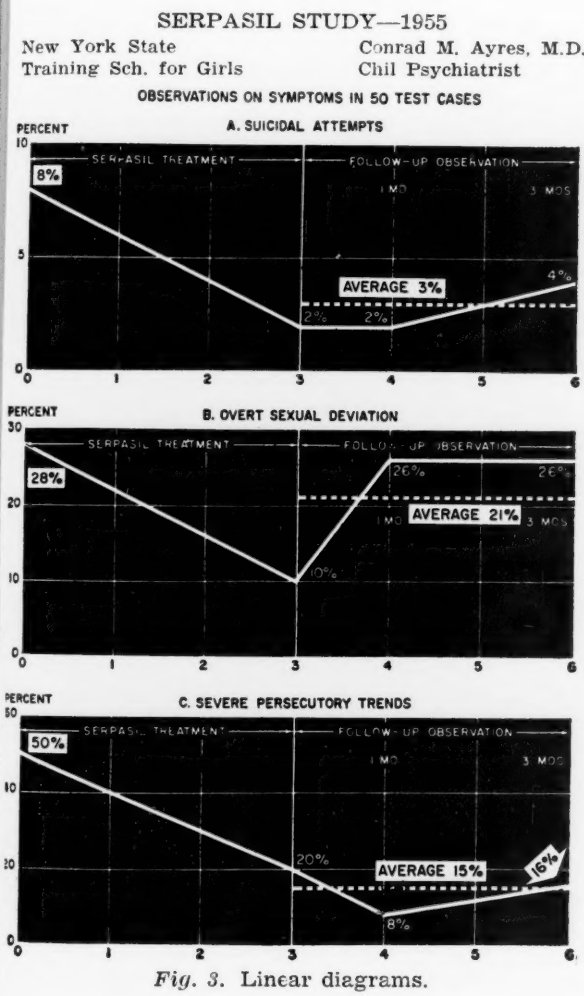


Fig. 3. Linear diagrams.

The diagrammatic line represents the variations of data, and is drawn more heavily than the background grid lines so that it stands out clearly. It indicates trends of events by the fluctuations of its level in relation to two coordinate lines, a horizontal one called the axis of abscissae, and a vertical one called the axis of the ordinates. The horizontal coordinate or axis of abscissae indicates time factors whenever these are under consideration. Figures indicating time values are placed below the axis of abscissae in correspondence to vertical grid lines. The ordinate or vertical axis represents values of percentage or degree, and may be prolonged below the point of intersection with the horizontal axis to represent negative values. Figures indicating percentages, degrees, etc., are marked at the left of the ordinate axis in correspondence to horizontal grid lines. Grid lines should be used sparingly so as not to distract visual attention, or detract from the statistical presentation.

More than one diagrammatic line may be used in a linear diagram, provided all diagrammatic lines in a given graph refer to the same individuals or groups. In this case, each diagrammatic line should have a characteristic design and should be properly identified by a caption with connecting arrow, or a footnote, or a key within the chart area. However, when too many diagrammatic lines are superimposed on a single graph, the clarity of the chart is impaired, and the goal of graphic presentation is defeated. When different individuals or groups are being considered, separate graphs are necessary.

By shading the area between the axis of abscissae and the diagrammatic line, one may transform a linear graph into what is known as a silhouette chart. This affords a striking visual contrast, especially when variations below the zero line, or negative values, are involved.

A special form of linear graph is the scatter diagram. Here, dots instead of a line are placed on the grid in relation to the coordinate axes. These dots represent the distribution of individual events or values. Usually the dots tend to cluster in the form of a path which follows a definite movement across the face of the chart. A line may then be drawn along this path to show the trend or direction of this movement. This type of graph is more suitable as a preliminary graphic aid rather than to furnish a final chart, except when emphasis on distribution of individual values or observations is essential.

Linear diagrams of any type are feasible

only when one is presenting homogeneous or continuous data without a break in the series. When showing data from discontinuous types of observations, namely, observations on different subjects, different forms of treatment, :different doses of medication, etc., the bar diagram or the circular diagram should be used.

Bar Diagram: The bar diagram gives visual contrast to various quantities by the comparative length of bars or solid columns.

BRONX AFTER CARE CLINIC PROJECT—1956

New York St. Dep't of Mental Hygiene — Conrad M. Ayres, M.D. Supervising Psychiatrist

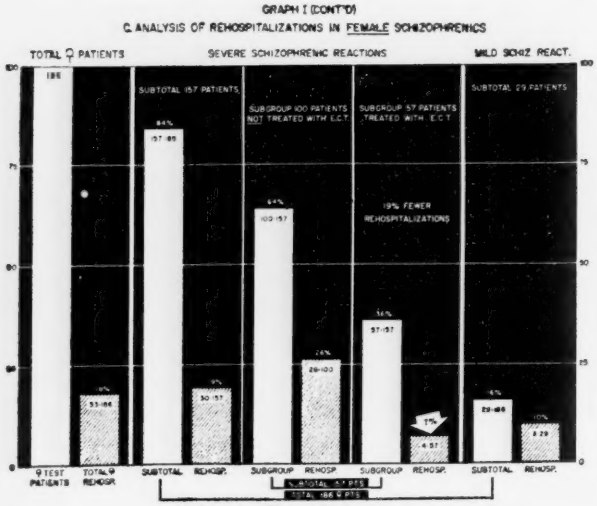


Fig. 4. Bar diagram.

The bar diagram, like the linear graph, is a rectangular form of diagram. The bars in the diagram may be constructed either parallel or perpendicular to the base of the page. Parallel and perpendicular bar diagrams are colloquially referred to as flag and chimney charts respectively. When a time element is involved, only the vertical type of bar diagram may be used, since a time element is always represented by the horizontal axis. Each bar may represent a percentage of the component parts, in which case the total bars will equal 100 per cent, or each bar may show the percentage of the sum-total in successive periods of time. Background grid lines and values of time, percentage, degree, etc., are also used in bar diagrams and the same principles apply to them here as in linear diagrams.

One may call attention to a particular bar or special portions of a bar by hatchings with parallel lines or by shading of different intensities. The hatching should preferably be diagonal because vertical or horizontal parallels may produce blurred images.

When the space between bars is eliminated, the so-called histogram is obtained. This, like the linear diagram, can be used only to compare variations of continuous elements in the same group of subjects. If the vertical lines in the histogram are eliminated, one obtains what is called the step diagram, whose function is similar to that of the linear diagram and the histogram.

Circular Diagram: This type of graph belongs to the group of sectional-area diagrams in which different sections of a geometric area are compared. Sectional-area diagrams should be used only to compare two or at most three components of a single total and when a changing time element is not involved. The significance of their various segments is expressed by legends inside, outside or below the chart.

The circular diagram is the form of sectional-area diagram generally used in medical writing.

BROOKLYN STATE HOSPITAL—SEPT. 1, 1958

Inpatient Population and M.D.-Inpatient Ratio

Fig. 5. A statistical graph.

In this type of graph percentage values are converted into degrees of circumference multiplying the percentage value by a conversion unit of 3.6 or by plotting percentages directly with use of percentage protractor.

The circular diagram is considered helpful in breaking the monotony of rectangular illustrations and in indicating at a glance the

proportion of the component parts to the whole. Diagonal hatchings, shadings of different intensities, or reversal of color of a particular segment of a circular diagram assist in focusing visual attention.

3205 Grand Concourse, New York, N. Y.

Acknowledgments: The author wishes to acknowledge the cooperation of Dr. H. H. Brill, Assistant Commissioner, New York State Department of Mental Hygiene, for allowing the use of the statistical data from Brooklyn State Hospital and the Bronx Aftercare Clinic shown in Figures 2, 4, 5 and 6.

The author wishes also to express his appreciation for the interest and generous assistance of Dr. Donald M. Carmichael, Director, Aftercare Clinics, New York State Department of Mental Hygiene.

Last but not least the author wishes to acknowledge his indebtedness to Dr. Nathan Beckenstein, Brooklyn State Hospital, for supplying the original data contained in Figures 2 and 5.

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Summary

The purpose of illustrative material is to lend clarity and interest to the text. Charts show easily comprehended information based on simplicity.

Work Sheet: The work sheet is the record of all the observations gathered throughout a study. It is a kind of catalogue which forms the basis for the construction of statistical tables or tables for publication.

Tables: The statistical table is a logical arrangement of data in columnar form. Its purpose is to emphasize specific relationships pointing out special trends. Tables should accompany and support graphs whenever the latter are part of illustrative material.

Graphs or Diagrams: Graphs are schematic representations of statistical tables. They interpret numerical data in visual form, emphasize the highlights of the findings and deliver the information quickly and clearly. The three main types of graphs used in medical writing are: linear, bar and circular diagrams.

1. Linear Diagram: The linear graph is a rectangular diagram on which varying quantities are expressed by a line, called the diagrammatic line. This line is plotted on a grid or background ruling, which facilitates visual evaluation in relation to a horizontal and vertical axis. Linear diagrams are feasible only when presenting homogeneous or continuous data without a break in the series.

2. Bar Diagram: The bar graph is a rectangular diagram which gives visual contrast to various quantities by the comparative length of bars or solid columns. Bar diagrams are used when presenting discontinuous data.

3. Circular Diagrams: The circular diagram is used preferably to compare two or at most three components of a total when a changing time element is not involved. The circular diagram is helpful to break the monotony of rectangular illustrations and to indicate at a glance the proportion of the component parts to the whole.

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The Psychiatric Armamentarium

(Available Forms of Psychiatric Treatment and Their Indications)

LEO ALEXANDER, M.D.

The criticism has often been made of psychiatric therapy that it attempts to treat illnesses whose nature is unknown with treatments whose effects are unknown. As far as the disease entities with which we are dealing are concerned, this is certainly true. As for the treatments, however, they are by comparison simple, provided we define their effects in terms of specific measurable changes that they induce, independent of the end result, in terms of the manner in which they influence the complex and probably multifactorial disturbances of the human mind and emotionality.

The most important feature in the planning and administration of rational therapy is diagnosis, not only in a general or global sense, but rather with specific emphasis on those parameters of diagnosis which are known to bear significant relationship to the established effects of treatments. Here we encounter the first difficulty. Diagnostic categories which we tend to use are formulated along Kraepelinian diagnostic and Freudian psychodynamic lines. By contrast, the majority of treatments, especially somatic treatments which we are using today, are unlikely to influence directly such complicated behavioral entities but rather certain specific and simple parameters of these disturbances such as excitation, inhibition, discrimination, generalization and the like. The development of objective tests to determine these simple, measurable parameters of mental disturbance is therefore of utmost importance.

A number of these have become available, notably the adrenalin-mecholyl test (Funkenstein[1]), the sedation threshold test (Shagass[2]) and the conditional reflex test[3,4] in which I have lately become increasingly interested. I find that the conditional psychogalvanic reflex is practically the most useful, can be easily established, is relatively stable and allows quantitative measurement. I find it reduced or absent in depressive states, returning to normal after successful therapy. In anxiety states, the reflex shows a variety of generalization phenomena. Equivalent, paradoxical and ultra-paradoxical phases can be clearly distinguished in both groups of patients. A point of interest is that the reflex shows a particularly high degree of differentiation between excitatory and inhibitory stimuli in acute early schizophrenic reactions while in the later stages of the disease disturbances appear to arise which we are about to subject to special study.

Refinement in diagnostic technique is of importance for the purpose of rational administration of drug therapy since it has been found that clinical response to a drug could often be predicted on the basis of a one hour conditioning session, thereby obviating a month's trial on a new drug. The correlation of the test result and outcome of therapy still requires further validation. We are at present undertaking such studies.

The refinement of clinical psychiatric diagnosis, likewise, is a requirement the importance of which has newly been impressed upon us as a result of our experiences with drug therapy. The rather broadly effective somatic therapies developed during the past twenty years—probably due to the fact that they all worked by rather generally diminishing the excitability of the higher nervous activity of the cortex[5]—have tended to blur the outlines of the disease entities in psychiatry which had been painstakingly drawn during the preceding one hundred years. Concurrently, the psychodynamic view that psychiatric disturbances were not diseases at all but rather reactions which differed in meaning, intensity and in terms of the patient's ego strength but not in nosologic specificity also tended to discredit nosology in psychiatry. The advent of highly specific drugs, however, forces us again to look for nosologic differentiation, a differentiation

From the Department of Psychiatry, Tufts University Medical School, and the Neurobiologic Unit, Division of Psychiatric Research, Boston State Hospital, Boston, Mass.

perhaps in terms of the brain mechanisms involved, rather than necessarily the disease process per se.

Further refined diagnostic differentiation of the psychiatric picture observed and of as many of its parameters as possible will enable us to make more varied and active use of the numerous therapeutic tools that are continuing to enrich our therapeutic armamentarium. Just as internal medicine had to move away from exclusive reliance on bleeding and purging, so we have to move away from exclusive reliance on one or two standardized treatments whether they be in the field of psychotherapy or somatotherapy.

At the present meeting as many of these areas will be covered as possible. For their most effective application, they must be applied according to specific indications, rather than in a stereotyped manner to illnesses of all types which has been such a compelling preoccupation in psychiatric therapy for so long. The less specific the treatment, of course, the more broadly effective it may seem in the greatest variety of conditions at the sacrifice, however, of degree of effectiveness.

Psychotherapy

Psychotherapy perhaps may be better defined in line with Horsley Gantt's[6] suggestion as "influence of the person upon the person" since that is its only consistent common aspect and perhaps even the only valid aspect. Hoch[7] and others have repeatedly shown that the results of the various methods of psychotherapy are remarkably similar in spite of their markedly divergent theoretical premises. There is need for more precise study of the actually effective objectively determined ingredients of psychotherapy. I have been particularly impressed with the elements of suggestion, mimesis of the therapist and identification with the therapist.[5] Milieu therapy is an increasingly important aspect of psychological influence upon the patient. Recognition of its importance came through group therapy and sociological investigations of the effects of hospital environment, such as those made by Stanton and Schwartz[8] for instance. Milieu and group therapy have grown through the newer remotivation techniques which we have discussed at last year's Institute and which will probably again be dealt with by Dr. Irving Rosen.

Electrotherapy

Electrotherapy, still the master treatment for depression, has undergone a number of metamorphoses and specialized variations since its introduction twenty years ago. Scientific studies of specific effects of quantitative variants of current on the nervous system have shed important new light on the problem. The different clinical psychophysiologic effects dependent on quantity of current were confirmed in animals by Peters[9] in a series of experiments which determined the effects of different quantitative variants of current upon conditinoing. I have dealt with this problem, which is essentially the problem of dosage in psychiatric electrotherapy, in my recent book.[5] Dr. Reiter has taken up the challenge posed by these quantitative studies of perfecting a unidirectional current so supercharged with additional high amperage spikes as to equal in effect that of high amperage alternating current. Yet because of the short duration of these spikes, thus keeping the average current rather low, he endeavored to continue to keep the side effects at a minimum. Validation of this innovation by study of groups of the most treatment-resistant involutional depressions and schizophrenic psychoses is yet to be undertaken, a very worthwhile research project considering its importance.

Another development of electrotherapy has been directed towards the perfecting of nonconvulsive stimulating currents which are non-painful and hence can be applied to the waking patient without preliminary sedation by barbiturates.[10] Dr. Eyres will report to this meeting his utilization of this method for therapy as well as for testing the perception level and tolerance level for this type of current which may become useful as an objective parameter of illness perhaps related to the phenomena of excitation and inhibition respectively.

Insulin Coma Therapy

This therapy is still of outstanding importance in the treatment of severe acute schizophrenic reactions since it is the least likely

to be followed by chronic residuals after termination of therapy.[11] Relapses and residuals particularly beset the treatment of acute schizophrenic states by means of tranquilizing drugs unless these conditions happen to be of the self-limited schizo-affective type whose recognition demands the clinical perceptiveness of the classical diagnostic schools exemplified by the studies of Kleist[12] and August Hoch[13] in particular.

It is my conviction, which I share with many clinicians in England[14] as well as in this country,[15] that insulin coma therapy has been too readily abandoned as a procedure available in public hospitals.

The New Psychotropic Drugs

Despite their limitations in the most severe illnesses, these new drugs have had by far the greatest influence on the transformation of psychiatric practice in and out of hospitals and on its results obtained. What these drugs lack in maximal intensive effect in comparison to other forms of treatment is apparently outweighed by the advantages of their ease of application and hence their availability to a large variety of patients. Kalinowsky[16] is no doubt right in stating that these drugs did not owe their introduction to advances in knowledge of biochemistry of the brain but rather to empirical serendipity. It was soon discovered, however, that the rational framework for their screening and evaluation was the conditional reflex experiment. Most pharmacologists and drug manufacturers used a modified conditioned avoidance technique along the lines of Masserman's method[17] for their evaluation and screening.

It is indeed in this area that the most striking correlations with their clinical effects can be observed. It is of interest that chlorpromazine, which is by far the most effective drug in schizophrenia, abolishes conditional reflexes rather selectively at dosage levels even before profound behavioral alterations are observable. As our studies mentioned above have shown, an almost over-precise responsiveness to conditional stimuli seems to characterize schizophrenic patients, particularly acute ones.[18] By contrast, chlorpromazine deepens depressive reactions whose characteristic Pavlovian parameter is inhibition of conditional reflex activity.[4] This inhibition appears to be further deepened by chlorpromazine administration. Meprobamate and benactyzine on the other hand release conditional reflex responsiveness; benactyzine by permitting excitatory generalization; meprobamate by enhancing inhibited positive conditional reflex responses and thus improving differentiation.[4] The combination of the two drugs is capable of restoring the inhibited paradoxical or equivalent conditional reflex responses of depressed patients and in the patients responding in this manner tends to relieve and bring about recovery from depressive reactions.

The only apparent paradox in this psychophysiological correlation is iproniazid. It appears to relieve the inert psychasthenic anhedonic depressions specifically[19] while having relatively little effect on the classical tormented self-reproachful depressions. Yet it is not a psychic energizer, certainly not in regard to conditional reflex activity since it appeared to inhibit conditional reflex activity in the three cases we have studied so far, similar to the effect of the phenothiazines. However, this problem requires further study in a greater number of fully recovered patients than we have yet examined by the conditional reflex method.

The psychotropic drugs are a particularly active, growing body in our armamentarium and their precise objective evaluation offers an increasingly effective and promising highly specialized tool to be used with specific target effects[20] in mind which can then be rendered more useful to the patient by additional correlated therapeutic efforts by other means.

The specificity and limited nature of the drug effects indicate that these drugs are not curative, but merely alleviate, counteract, control or compensate for certain spesific symptoms which may be crucial either in the chain of disturbances evoked by the disease or in the psychic economy of the patient. Thus chlorpromazine appears to have a specific effect upon manic drive, as well as the panic, drivenness and tension of the schizophrenic; meprobamate and benactyzine upon the ruminative self-torturing depressive drive, and iproniazid upon psychas-

thenic-anhedonic inertness. The drugs thus allow the patient to carry on until the self-limited disturbance subsides. In not self-limited diseases, discontinuance of the drug precipitates relapse, or rather reappearance, unmasking or decompensation of the disorder.

Frontal Lobotomy

The acceptance of the fact that there is such an event as a patient having failed to respond to any of the systematic and skillfully applied forms of therapy—while distasteful and painful to most therapists—nevertheless must be straightforwardly faced. It is important to know then that the only treatment in psychiatry, apart from malaria therapy of neurosyphilis, that ever earned the Nobel prize, namely frontal lobotomy, still offers a significant chance for a therapeutic result of high quality. I have had to face this impasse in eight patients since the introduction of the new psychotropic drugs in June, 1954. Modified operation adapted to the severity of the patient's illness led to complete and/or social recovery in four of these cases; marked improvement out of hospital in two; moderate in-hospital improvement in one case; while one patient remained unimproved. A full account of one of the patients and details of the others in table form are presented elsewhere.[5]

It is my conviction that frontal lobotomy remains an important and effective item in our therapeutic armamentarium and sometimes the only one that can resolve the illness in truly desperate treatment resistant cases.

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Effectiveness of Various Electro-Stimulative Technics

CHARLES BUCKMAN, M.D., MAURICE FENICHEL, M.D., IRVING PINSLEY, M.D., and JOHN M. ERDOS, M.D.

In present day treatment procedures we find two main schools of thought: One feels that the old procedures have always been good and adequate, while another large group recognizes disadvantages in the old procedures and has actively attempted corrective measures. This discussion is concerned with the presentation and evaluation of newer methods from the standpoint of both clinical value and increased safety in clinical application.

Although newer drug procedures have preempted our thinking recently more mature clinical evaluation makes it evident that the somatic, including electrical, therapies occupy a strong position in our therapeutic armamentarium. The oldest of these is still electroconvulsive treatment and its various modifications. We now find that innovations in uni-directional treatment currents make possible stronger therapeutic doses than have been possible in the past. We have even been able to convulse with the new uni-directional current patients who had not responded to alternating current. Furthermore we find that some patients respond faster than with alternating current and even the quality of the response is improved. When we search for a reason for this improved therapeutic responsiveness, we find that the side effects of physical thrust, apnea, confusion and fear of treatment have been considerably reduced. Apparently we have found a means of utilizing the full effect of the treatment dosage in the therapeutic direction instead of wasting part of its effectiveness in creating side effects.

Convulsive therapy remains a definitive treatment. However, there are many long-standing hard core types of patients who require more than is offered by convulsive therapy alone. This has long been recognized and even our improved and stronger convulsive treatments with the recently developed uni-directional currents do not obviate this fact. In the past we have been compelled to rely on repeated deep insulin coma or lobotomy as more drastic or more thorough forms of approach to this problem in a hospital setting. Furthermore, the occasional irreversible features of psychosurgery have developed many opponents to this approach. For these reasons we have spent considerable effort in developing the clinical value of an alternative therapeutic approach known as electrosleep therapy. We and others (Epstein and Campden-Main) have already presented and published some of our results in this direction. Some observers may find it easier to relate this technique to so-called "electro narcosis" which appears to be a less flexible form of treatment. It is pleasant to report that we now have a still more delicate, safe and easier form of treatment—"Deep Sedac Therapy."

This treatment uses powerful Sedac currents. As is known, Sedac is meant to stand for "sedative action," a useful term in discussing the treatment with patients or relatives. Fortunately the term is suitable for describing the actual treatment, as well as the calming after effects that the patients experience. In addition, the sedative action carries still further since it is relatively easy and safe for the doctor to administer, far safer than our former techniques. This element of safety cannot be over emphasized and it is hoped that our demonstration will make it clear that we have excellent control throughout the treatment, despite the fact that the patient remains deeply unconscious during the greater part of the treatment. The patient responds quickly at the end of the treatment, so that we may feel reasonably certain of his good physical condition.

The deep Sedac treatment is applied with the initial induction of barbiturate or grand mal to help establish full anesthesia depth. When barbiturate is used, we measure the exact amount necessary to initiate anesthesia

From Kings Park State Hospital, Kings Park, New York.

by stimulation with the Sedac current as first described by Impastato. In this way we avoid undue side effects and are able to establish and maintain a deep, yet safe, state. When we use the convulsive introduction, we start with a uni-directional grand mal, and sometimes we even add a second grand mal before continuing with deep Sedac treatment. Immediately after the grand mal we stimulate the breathing and then continue with the deep Sedac currents. We use the newer blue bulb for adequate dosage and record the number of Sedac units applied: If some embarrassment of breathing or pulse occurs, we reduce the intensity somewhat to allow for comfortable deep treatment. We have found it possible to adequately control side effects in this way and thus to insure safety in treatment.

The most recent addition to our armamentarium is the method of measurement which has been discussed by others (Eyres, Heller in this meeting). It is hoped that our insight into the nature of the illness will greatly improve in the future through these measurements and enable us to determine the points or pathways which measure inadequate responsiveness. These new measurement procedures have already been carried far enough to allow us to see that adequate treatment is accompanied by gratifying clinical improvement. We have every reason to hope and expect that our therapies will be based on more scientific substance than we have been able to evolve in the past.

Description of Currents

The current selector knob of the Reiter SOS Stimulator has eight positions with which we can select one of five uni-directional currents, or one of three Sedac currents. The uni-directional currents of this machine can be seen in the oscilloscope. They consist of about 30 groups of pulses in each second. Each group of pulses contains approximately 25 individual pulses. Each individual pulse has very steep walls, so that it rises and falls at a rapid rate. In addition, the pulse top is flat at Position 1, and becomes increasingly sharper as we progress to Position 5 which has the sharpest or spikiest rise, with a time duration of the spike lasting a fraction of a millionth of a second. It is these spiky currents which are used to establish the brain discharge called a convulsion. The flat topped currents are also able to cause a convulsion, but are less efficient in doing so. To sum up, the convulsive current may be analyzed along mathematical lines and broken up into a sum of many frequencies, from the 30 per second of the group combinations to the millions per second of the sharp spiked portions of the individual pulses.

The second type of current we can choose with the Current Selector knob is the SEDAC or sedative action currents. These are a selected portion of the alternating currents we have just described, and contain only the high frequency portion, say from a million cycles and up. They have the advantage that they can stimulate powerfully below the pain threshold. In addition, we have three calibrated scales so that we can measure the amount applied or needed from 0 to 10, or 100, or 1000 units.

Summary

Although various newer drugs are used extensively, the older somatic therapies are continued with excellent results, particularly in a hospital setting. By following definite clinical criteria we exercise selectivity for the various treatments. Illness of acute nature and of comparatively short duration, in younger people with adequate educational, cultural and social backgrounds, and who present a preponderance of abnormal ideational content respond best to insulin coma. The many depressions that we know of still respond best with modified electroconvulsive therapy. In refractory, long-standing cases of this latter type, metrazol convulsive therapy combined with muscle relaxant gives good results.

For the cases that did not respond to all known therapeutic approaches, particularly the long-standing hard core paranoid states, electro sleep stimulation therapy gives excellent results and warrants continued use of this form of treatment, except that a change in the type of current was initiated since July 1958 through the use of the Sedac high frequency currents. This latter technique is safer and simpler and may be used

as an office technique, whereas the previous uni-directional current was considered best handled in a hospital setting. It is well understood, of course, that other therapies, such as various activity programs and psychotherapies play an equally important part in the total approach to psychopathology of any sort and that follow-up care will frequently sustain adequate adjustment and prevent relapse.

ADDENDUM

In August 1957 we reported a total of 106 cases treated with uni-directional electrosleep therapy of which 26.4% hard core cases were released from the hospital and an approximately similar number showed fair to good improvement in hospital adjustment.

Since the use of the Sedac current electrosleep technique, an additional 81 hard core type cases were treated, of which 32, or approximately 40%, were released from the hospital on convalescent care, and about an equal number have shown good improvement in hospital adjustment, making the patient more receptive to further psychological and rehabilitative measures. This treatment appears to improve the triad of emotional—endocrine—autonomic imbalances, resulting in better total homeostasis and leading to more adequate reality testing and environmental readjustments.

Author's Note: The Sedac Stimulator described is manufactured by Reuben Reiter, New York, N. Y.

The Present Status of Insulin Shock Treatment at Brooklyn State Hospital

MILTON E. SCHWARTZ, M.D.

The discovery of chlorpromazine and other tranquilizers opened a new era in the management and treatment of mental disorders and seriously affected the insulin shock therapy regime at this hospital. Chlorpromazine was first used in New York State hospitals in 1954.

Insulin shock therapy has been in use at Brooklyn State Hospital for over 20 years under a standardized regime as follows: At first, insulin shock therapy was conducted in a separate unit divided into male and female wards, each with a resident psychiatrist in charge. The female ward had 24 beds; the male 40 beds. The treatments were administered in accordance with the Sakel method with certain modifications. The nursing personnel assigned to each unit was well trained in this therapy. In the very early years termination of coma was accomplished by gavage. Later intravenous glucose 33⅓% solution was substituted. Until late in 1954 the Male Service usually treated 30-35 patients at a time. The Female Service treated about 24 patients. Follcwing introduction of the chlorpromazine derivatives there occurred a noticeable drop in the number of patients referred to insulin shock therapy. Due to this it was decided that the insulin shock service should be removed from its autonomous position and placed with the Reception Services on their respective male and female wards. The insulin section was limited to 10 patients. Insulin shock therapy as an integral part of the Reception Service began on Oct. 2, 1956. I have been in charge of the Male Insulin Ward since the aforementioned date. The only change since the inception of treatment has been the addition of four beds to the Male Service in order to shorten the waiting period. Now we are treating 14 male patients in this ward. There has been no increase in patient load on the Female Insulin Service.

Since October 2, 1956 we have treated 96 patients. ranging in age from 16 to 34 years and in the following diagnostic groups:

1. Paranoid schizophrenia	38 patients
2. Catatonic schizophrenia	31 patients
3. Mixed schizophrenia	17 patients
4. Simple schizophrenia	3 patients
5. Hebephrenic schizophrenia	4 patients

None of these patients had ever been treated with insulin previously. However, there were some that had previously had electric shock therapy. For the most part we tried to treat patients who were acutely ill, those having an initial psychotic episode, and those with the most acute symptoms.

In this series, 68 patients showed general overall improvement: 27 patients showed marked improvement, while 41 showed moderate improvement. All of these patients were either discharged outright or placed on convalescent status. Four patients have been returned to the hospital in relapse. The other 64 patients remain sufficiently improved to be adequately maintained on the outside; 26 patients were listed as unimproved and if we add to this the four patients who relapsed, we have 30 patients as unimproved.

There were no treatment deaths or serious complications encountered in this series. One patient on convalescent status committed suicide and one other patient was removed from treatment because of a marked allergy to insulin.

We have used combined insulin-electric shock therapy in 20% of this group, and have found it to be extremely beneficial in the more severe, regressed, catatonic patients who retained infantile regressive features in their behavior after 15-20 comas. One method was to give sub-coma insulin and electric shock in combination twice a week until 10 treatments had been completed.

Our treatment routine calls for insulin to be administered daily for five days per week in doses beginning with 15 units of regular insulin and increasing at the rate of 10 or 15 units per day until coma dose is reached. There is a fair variance in this method. The schizophrenic is particularly resistant to insulin and we have had to use doses as high as 720 units to attain coma. Once this is achieved a zigzagging of the dosage usually produces a coma at a lower dose. We attempt to maintain a maximum of 150-200 unit dosage. The course of treatment is lengthy as our aim is that each patient have 50 adequate comas. We usually use a low dosage rest period after three successive deep comas. The patients are terminated at the pre-convulsive stage or after being in moderately deep coma for more than an hour. The entire process from drowsiness to termination is about 2½ hours.

In the therapeutic milieu, stress may be placed on group unity, cooperation and establishment of adequate relationships between the patients on treatment. Group therapy meetings are held once a week in a conference room on our convalescent ward. Here free and open discussions are stimulated and group productivity is encouraged and aided. Private interviews are also scheduled during the after hours. These interviews help patients learn to be more aware of their feelings and reactions and regain confidence.

Summary

At present insulin shock therapy is being administered along with other treatment on the Reception Service of this hospital. In this most recent series 96 male patients were treated without untoward incident. There was overall improvement in 64 patients, 27 showing excellent recoveries to this date. Thirty patients were unimproved and nearly all of these remain in the hospital, maintaining a poor functional level which is tolerated by the family so that they can remain at home. This treatment was of no help in the hebephrenic group treated here. Insulin shock treatment appears to have a wide margin of safety, with rare complications. Our percentage of improvement with patients discharged or on convalescent status to this date averages 66%.

In view of our findings insulin shock treatment still appears to be an extremely valuable therapeutic tool in the hospital treatment of the young, acutely psychotic schizophrenic.

Brooklyn State Hospital, Brooklyn, N. Y.

Present Statues of CO_2 Therapy* (A Summary)

L. J. MEDUNA

The psychiatrists in the Illinois area pooled 900 patients treated with carbon dioxide. All these patients were given the self administering Jackman's neurotic index which explores only symptoms and not nosologic entities. The index consists of 54 symptoms graded from 1 to 4 according to severity. The patients were given the index before treatment began, after the 20th treatment, and at the termination of treatment. The scores were then compared. When the total score was reduced 95% or more the patient was considered recovered; from 50% to 75%, the patient was considered greatly improved; from 25% to 49% the patient was considered slightly improved, and any change less than 25% was not considered improvement at all.

Based on this scale 60% of the patients recovered, 18% were greatly improved, 6% slightly improved; 16% did not improve and 3% of these became worse. The following list shows the percentage of improvement of those symptoms which responded best to CO_2 therapy, as measured by percentage decrease in the neurotic index score.

PERCENTAGE DECREASE OF JACKMAN'S NEUROTIC INDEX SCORE

SYMPTOM	Percentage
Anxiety	84%
Asthma	85%
Constipation	81%
Lack of cencentration	86%
Family inter-personal differences	94%
Guilt feelings	81%
Indecision	94%
Indigestion	75–90%
Irritability	75–90%
Inferiority	75–90%
Impulsiveness	75–90%
Insomnia	75–86%
Instability	75–86%
Nailbiting	75–86%
Phobias	75–90%
Tension	75–90%
Vaso motor disturbances	75–90%

Another cooperative study was made on an IBM punch card system. This punch card contained 56 different symptoms and had about 60 to 70 variables. The questions covered among other things the patient's medical history, economic status, number of children, duration of illness, severity of symptoms, age, social status, body build, psychologic type diagnosis etc. Twenty-five psychiatrists were invited to participate in these projects. Of the 25, five refused to participate for the reason that they did not believe in the treatment. Three others did not participate because they did not believe in the usefulness of the punch card system. For the 17 that participated there was a pool of 666 patients.

The following are results which were obtained from the IBM machine. Overall improvement was 68%. This contrasts with a 62% figure reported in 1947. Treatment with psychotherapy alone gave an overall improvement rate of 50%. The drop out rate was 32% with CO_2 and 40% with psychotherapy. The average number of CO_2 treatments was 40.

The following factors had no influence on the results of CO_2 therapy: Sex, age, race, marital status, body build, duration of illness, severity, previous treatment, diagnosis.

CO_2 showed better results than expected and psychotherapy poorer results in the following: Anxiety, dependency, self consciousness, guilt feelings, headache, tension, indecision, inferiority, blocking and instability.

CO_2 and psychotherapy gave worse results than expected in the following symptoms: Fatigue hypochondiasis, insomnia and suspicion.

There are many interesting and unusual applications of CO_2 therapy. Brick's treatment of prison neurosis in which he obtained results as outlined above. McCrea has used the treatment very successfully during labor; in 200 deliveries he had only three miscarriages; while in 200 deliveries without CO_2 he had 21 miscarriages. McCrea also used CO_2 for children age 2 to 14 for various types of psychologic illnesses. He has treated 75 such children; 47 recovered and 23 improved greatly, three discontinued treatments; two were unimproved.

*Abstract by Dr. David J. Impastato of paper delivered by Dr. L. J. Meduna at annual EPRA meeting.

Problems of Indications as Viewed by a Psychoanalyst

RUDOLPH M. LOEWENSTEIN, M.D.

In this presentation I should like to submit facts and considerations derived mainly from my own experience. My clinical work consists largely of psychoanalytic treatment. In addition, but to a much smaller extent, it is devoted to interviews with patients who seek advice whether they should be psychoanalyzed or whether they should continue analytic treatment or psychotherapy even when no good results are forthcoming. I should like to discuss these consultations and what enters into the decisions about such patients.

First it may be useful to refer briefly to Freud's opinions with respect to indications for psychoanalytic treatment. He regarded psychoanalysis as the treatment of choice mainly for symptom neuroses of the three well known types: hysterias, anxiety hysterias and obsessive-compulsive neuroses. Freud warned against the use of psychoanalysis in treating psychotics and was sceptical about its chances of curing sexual perversions. According to him, not even all typical cases of psychoneurosis were to be analyzed. The prognosis was not considered good for patients older than the forties, or for extremely severe neuroses. On the other hand, in cases of mild neurosis the psychoanalytic treatment was deemed too complicated and too costly in time and money, since such patients could be helped more economically. Moreover, to be successfully analyzable, a neurotic patient should possess a relatively stable ego enabling him to form what Freud called the "therapeutic alliance" with the analyst, as well as to withstand the inevitable frustrations of his transference wishes. Freud described an additional type of circumstances that might contraindicate psychoanalytic treatment; namely, the realities of a patient's social and familial situation. As an example, he mentioned a female patient who was married to a wealthy man and had several children. Because of numerous neurotic symptoms this woman had undergone treatment in sanitaria for varying lengths of time. She was unhappy in her marriage and deprived of any sexual satisfaction; to stay in a sanitarium was an escape from her frustrating marital situation and a mild, indirect compensation for it. Freud thought that in such a case psychoanalytic treatment would be a needless cruelty. It would force the patient to face the possibility of divorce from a husband on whom she was financially dependent. Moreover, in Austria before World War I, divorce would have meant social ostracism and the loss of her children.

Thus, in Freud's opinion, contraindications were numerous and the range of cases where psychoanalytic treatment could be successfully applied was limited. But once, in a mood of optimism after the end of the first world war, he foresaw the use of psychoanalysis combined with other psychotherapeutic methods for a much larger group of patients. However, psychoanalysis came to be applied more widely; whether because therapeutic results were achieved in other types of disorders, or because of a greater optimism on the part of some disciples of Freud, or because in the last few decades more neurotic behavioral or character disorders were diagnosed than mere symptom neuroses.

Today psychoanalysis or psychotherapy is used for a wide variety of disorders encompassing psychoneuroses, psychoses, borderline cases, sexual perversions, character neuroses, delinquencies and various behavioral problems, difficulties in social and marital adjustment, as well as for psychosomatic disorders. This "widening scope" (Stone) of analysis or psychotherapy has led to a number of brilliant successes. It has also brought in its wake a number of failures and painful disappointments.

As a result it became clear that schizophrenia could be analyzed, if at all, only by a method so essentially different that one may question the scientific validity of calling it by the same name. Freud's theoretical distinction—that the pathogenic conflict in neurosis is between the ego and the instinctual drives, whereas in psychosis it is between the ego and external reality—found

confirmation in need for this fundamental difference in therapeutic technique. And we know that even such basically modified methods cannot be relied upon to bring about stable results in schizophrenia. Many a disappointment in the result of psychoanalytic treatment must be ascribed to a failure of diagnostic distinction between psychoneuroses and the so-called borderline cases. The latter, indeed, also require considerable modifications in the therapeutic technique for satisfactory results (Knight).

Particularly difficult problems of indications are presented by the so-called character neuroses. These encompass a large and heterogeneous group of disorders whose treatment does not lead to homogeneous results. Character changes that are favorable from the point of view of a patient may, sometimes, create a great deal of dissatisfaction on the part of his environment. Thus when a meek and submissive obsessive-complusive patient becomes self-assertive and active as a result of his cure, his wife may well complain bitterly about such treatment. To repeat, in cases of character disorder it is often especially difficult to decide whether psychoanalysis is indicated or not. A disorder which appears unimportant to the outside world may be highly important to the patient, and a favorable change in that area might achieve significant consequences for his personal life and work. On the other hand, a treatment as costly in time and money as psychoanalysis will hardly prove justified if it accomplishes only insignificant changes or no results at all. I do not know of a ready answer to these problems, and the dilemma has to be solved, as best one can, in each individual case.

A somewhat similar problem arises when a decision must be made between continuation and interruption of a psychoanalytic treatment. I treated a young woman for depressions with suicidal tendencies, outbursts of pathological jealousy and violent rages against her children. After several years of analysis, the disappearance of her symptoms and a favorable change in her personality caused me to advise an interruption of the treatment, with the possibility of resuming it should the need arise again. Neither the patient nor her husband wanted the treatment halted. They were not so much concerned with a possible recurrence of symptoms as with the fact that there were still moments when the patient was irritable and had arguments with the husband. For better or worse, I refused to continue; and I have not seen the patient since. While I do not know whether my decision was the best possible one, I believe it was sound. I arrived at it for the following reasons. The remaining reactions of this patient, including her irritability, seemed to be within the limits of what must be considered "variations of the normal." And I felt that in the patient's and her husband's wish for still more change I could discern a "quest for perfection," for a perfection which can hardly be expected to result from even the most thorough psychoanalysis. This "quest for perfection" is but one facet of the many expectations we encounter among patients in psychotherapy or analysis. Let me give you another example of such unrealistic expectations.

Years ago I analyzed a journalist, a man in his early forties, who suffered from a serious neurotic depression and lifelong potency disturbances. After successful conclusion of treatment he left for another city and I did not see him again for several years. He was very satisfied, successful in his work, and there had been no recurrence of symptoms. And yet, he was reproachful about his analysis: it had not made him a creative writer. Now, no surgical patient would reproach his surgeon because an operation did not turn him into an athlete when he had not been one before. But some psychiatric patients do expect not only to be cured of their illness, but also to be made successful, rich, and happily married. When I mentioned just now that my patient had become very successful in his work, I did not mean to attribute this directly to his treatment. What the analysis did was merely to cure his neurosis which had blocked the use of his pre-existing intelligence and talent. Without these personal abilities no treatment, in itself, could have made him a success.

Unrealistic expectations of this kind unfortunately are shared also by some psychiatrists. Consciously or not, they see in psychoanalysis a sort of panacea for all human

ills, even those which do not properly belong to the domain of psychiatry. Unrealistic expectations likewise have crept into the new field of medicine which psychoanalysis helped to open up: psychosomatic medicine.

As a young student I once spoke to Karl Abraham about a patient who presented a difficult differential diagnostic problem. I stressed the patient's neurotic behavior, to which Abraham wryly remarked: "A patient can have both a neurosis and a neurological disorder." A few years ago I was consulted by a colleague who had been advised by several psychiatrists and internists to undergo a psychoanalysis because of anxiety attacks. He wanted to know whether I concurred in their opinion. His anxieties had, at first sight, the character of an agoraphobia. And yet the symptomatology, as it emerged in several interviews, differed from that described by other phobics. There was something flat in his description of the symptoms and of the conditions under which the attacks would appear, that did not seem to have any plausible bearing on these symptoms. Among other things he mentioned to me that he had an adenoma of the thyroid. I advised him to have the adenoma removed as there was a danger of a malignancy and also because his symptoms did not seem entirely characteristic of a neurosis. It did not surprise me when he told me, after the operation, that his anxiety attacks had disappeared completely.

Some time ago I heard about a patient who had been in psychotherapy because no organic lesions had been found to explain his back pain; and then, one day, a tumor of the spine was discovered. From this and similar cases the conclusion is obvious that a seeming absence of lesion does not by itself justify a diagnosis of neurosis and an ensuing psychotherapy, but that a positive diagnosis of neurotic disorder must be made before such treatment can be properly recommended. In former years, psychoanalysts needed the cooperation of reliable medical consultants in order to make sure that a patient's resistance would not be unduly increased by his doctor's possibly hostile distrust of psychoanalysis. By contrast, nowadays we need such cooperation to make sure that our patients will receive serious medical examination. Indeed, many of us have had the unfortunate experience that some internists are so impressed by the role of emotional factors that they forget the possible coexistence of neurosis with an organic disease, or that they overlook the intricate interactions between the somatic and the psychic. Let us take the duodenal ulcer as an example.

In a paper entitled *Physiologic, Psychologic, and Social Determinants in the Etiology of Duodenal Ulcer,* I. Arthur Mirsky recently presented a brilliant and penetrating synthesis of the modern research so far done on this subject. The following statement is quoted from his conclusions:

> ". . . an attempt has been made to delineate only a few of the links in the chain of events that comprise the physiologic, psychologic, and social determinants in the predisposition to and precipitation of duodenal ulcer in man. Such a survey makes obvious that there is no single causal agent in the etiology of this syndrome and that the discrepancies that exist between various hypotheses are related to each proponent's particular orientation. Those who insist that the development of duodenal ulcer is determined solely by 'organic' factors are as fallacious as those who claim that 'psychic' factors are the sole determinants."

From these findings, then, it clearly follows that in the treatment of duodenal ulcer patients a full and understanding cooperation between psychiatrist and internist is indispensable.

As a further example, permit me to describe the intricate, reciprocal interaction between physiological and psychological mechanisms and their place in the treatment of a case of anxiety hysteria. For the sake of brevity, I shall present only the part of the patient's psychopathology relevant to this discussion of psychosomatic disorders. The acute anxiety attacks started in adult life, as a result of a fainting spell in a department store which was followed a few days later by the death of a close friend of the family. This incident was in the foreground of the patient's mind as the causation of her anxiety attacks. When I started to treat her she would have these anxiety attacks several times daily, under various conditions. More careful study in the setting of a psychoanalytic treatment revealed two types of anxieties; one was rather in

the nature of a fear of anxiety, the other a more direct, uncontrollable anxiety and "jitteriness." This second type was diagnosed by the internist as based to some extent on mild hypoglycemic states. He prescribed a diet which the patient followed reluctantly. The psychoanalytic investigation, in turn, was able to uncover the unconscious motives for her peculiar dieting habits. The patient had a fear of gaining weight, which unconsciously was based on an ambivalent attachment to her mother, on fear of becoming feminine like the mother, on fear of thus indirectly competing with her. By being thin, she remained, so to speak, a little child who could ask and obtain the mother's protection and forgiveness for her guilty wishes. These guilty wishes had been intensified by the death of her husband's friend. Thus her fear of gaining weight led her to eating habits resulting in hypoglycemic states which provoked excessive anxiety. This, in turn, left her with increased fear of helplessness, with an increased unconscious need for the mother's protection, thus again reinforcing her fear of gaining weight. Without the correct medical diagnosis and the prescribed dietary changes, it would probably have been impossible for the psychoanalyst alone to break this vicious circle. To understand this fully took me a long time.

The reformulations of psychoanalytic theory by Freud in the 1920's have had a favorable effect on the further development of the psychoanalytic therapeutic technique. Particularly since the publication of Anna Freud's work, analytic technique has made considerable progress. The successful treatment of adults, adolescents and children is possible now in cases that previously would have been inaccessible to analysis. For example, very fine successes with severely depressive patients were reported by Edith Jacobson. The knowledge of ego psychology has not only enlarged the sphere of our effective therapeutic endeavors but has also made them more precise and complete.

In certain instances, our vastly better understanding resulting from this increased knowledge of ego psychology has led to distinct modifications of psychoanalytic technique. I mentioned already the treatment of borderline cases. Robert P. Knight writes about this type of patient as follows:

> "With our analytic knowledge we can see how he defends himself, and what he defends himself against, but we do not attack those defenses except as we may modify them or educatively introduce better substitutes for them. Our formulations will be in terms of his ego operations rather than of his id content, and will be calculated to improve and strengthen the ego operations."
>
> "The term borderline case is not recommended as a diagnostic term, for a much more precise diagnosis should be made which identifies the type and degree of psychotic pathology. Far more important, however, than arriving at a diagnostic label is the achievement of a comprehensive psychodynamic and psychoeconomic appraisal of the balance in each patient between the ego's defensive and adaptive measures on the one hand, and the pathogenic instinctual and ego-disintegrating forces on the other, so that therapy can be planned and conducted for the purpose of conserving, strengthening, and improving the defensive and adaptive functions of the ego."

Even in cases that fall within the general framework of psychoneuroses, particular forms of ego disturbances may make it necessary to introduce some modifications or variations (Loewenstein) or "parameters" (K. R. Eissler) in the use of psychoanalysis, without which therapeutic results would hardly be achievable.

Despite the manifold progress attained so far, we still do meet with some disappointing failures even in cases that, at first sight, we hoped to find amenable to cure or improvement through psychoanalysis. A promising comprehensive study has been started by a group of analysts at the New York Psychoanalytic Institute, with the aim of describing the causes of therapeutic failure more precisely and of translating this knowledge into clinical signs that might permit their assessment before the start of treatment.

I spoke before of the problem one has in evaluating whether the analysis of a case ought to be terminated or continued, and, if the latter, whether with the same or another therapist. In my experience this difficulty of evaluation is immeasurably greater when the patient has been in treatment with a colleague whose training and method of work are unknown to me. Psychoanalysis

is fashionable nowadays for patients as well as among psychiatrists, and the term is used even when the type of psychotherapy applied in a given case is very different from what I would call psychoanalysis. To be sure, psychoanalytic treatment bears no trademark and cannot be strictly delimited, no more than surgical treatment can be defined in too narrow a sense. But the indiscriminate use of the term psychoanalysis makes scientifically valid comparisons impossible.

Psychoanalysis is not only a form of psychotherapy, but also a body of knowledge and the only existing comprehensive theory of personality. This endows the psychoanalytic therapeutic technique with a rationale, with a scientific background that is unfortunately absent in other forms of psychotherapy. A comparative study of various psychotherapeutic methods is being made at the Treatment Center of the New York Psychoanalytic Institute by a number of analysts under the leadership of Drs. Heinz Hartmann and Leo Stone. It will, we hope, some day lead to the establishment of clear-cut criteria for different types of psychotherapy, from the vantage point of psychoanalytic theory.

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Appraisal of Milieu Therapy

IRVING M. ROSEN, M.D.

We all recognize the importance of milieu (which in this usage is another word for environment) in the careful consideration we give to purchasing a home. We have always manipulated the milieu in our hospitals, in transferring patients about for one reason or another and there have been, at least since the time of Pinel, papers which have focused on the milieu as a therapeutic force. But now there has been a converging of anthropology, sociology, industrial management, sociometry, and architecture too with psychiatry. Milieu studies are far more sophisticated and better organized than ever before. Books and articles and new journals are pouring off the press in a tidal wave, and the authors, most of them, act as if they had hold of something really exciting and significant. Most likely they are right, although proof of the effectiveness of the milieu approach is no easier to demonstrate to the full satisfaction of the skeptic than that of any other therapy, particularly at this stage of exploration when enthusiasm and preliminary results carry us along.

I will try, in this paper, to show what evidence we have that the milieu itself contains a potent medicine, which may be used for good or for bad. Milieu therapy may be defined as the use of the human and physical environment of the patient as a treatment tool. Following are some of the significant components of the milieu: the beliefs and attitudes and orientations of the human beings in the institution or community; the organization of this conglomerate and the communication within it and with other conglomerates and individuals outside it; leadership; the grouping of the patients; the ways of using the team; the roles, flexible and stereotyped, assumed by the members of the team and the patients; and the nature of their motivations.

We can learn about the milieu by means of opinion polls; observation, participant and non-participant; from patients and personnel whether in individual or group therapy or in other group meetings; by the comparison study of various institutions; by sociometric experiments; and by the study of situations not deliberately planned. The milieu may be manipulated in many ways: through management and administrative techniques such as shifting patients and personnel about; through variations in leadership patterns and various methods of decision-making whether autocratic or democratic; through programming and planning; through the facilitation of communication; and through ways of delegating and controlling authority. By now it can be inferred that milieu therapy does not conform to the definition of an ideal therapy. It is not simple, compressible into pill form, or easily and uniformly prescribed. It is not easily learned about and it is probably not even teachable to all students. However, and this is important, it is not optional; milieu is always present. It will operate with us or against us and it behooves us to know as much about it as possible. Because it is always present it is always available. No matter how much we lack personnel and funds and the facilities for other treatments, there are two things present in every hospital—patients and environment—and both may be used therapeutically.

I cannot spend the time on the definition of sociological terms and on the details of the use of milieu therapy. I must get on to the appraisal. I will review some of the writings of therapists who have used this therapy and have evaluated it. There are papers giving evaluative impressions and those that use figures. It is difficult in some instances to separate the milieu effect from the effect of other treatments, particularly drug treatment. Some investigators consider that the addition of personnel and the heightening of activity constitutes a milieu therapy, others have measured pure manipulation without the addition of new people or new facilities. Harry Stack Sullivan,[1] at Sheppard and Enoch Pratt Hospital, from 1929 to 1931, paid particular attention to the personnel who impinged on his patients in

an effort to create a therapeutic milieu. He reported markedly favorable results in individual cases. Rioch and Stanton[2] state that in Sullivan's milieu the recovery rate as measured by return to home or work, of young, first-break male schizophrenic patients was better than 85% and continued at this level for several years after Sullivan himself had left. Myerson and Tillotson[3] reported in 1939 that all patients on their total-push program improved, though none recovered. Their program focused on four elements in the patient's environment. (1) Improved medical and physiotherapeutic treatments; (2) exercise and games; (3) use of reward and blame; and (4) diet and vitamins. A particularly important study was that of Anna Freud and Dorothy Burlingame[4] during the second world war. Their group organization was changed from a community with nurses for all children to one in which each nurse took the role of substitute mother for a group of four or five children. The result of this simple change in arrangement was astonishing in its force and immediacy—to use the words of Anna Freud. Following a couple of weeks of emotional dynamite when a great deal of anxiety and possessiveness and jealousy broke out, a quieter, more stable and comfortable situation obtained and the children began to develop in leaps and bounds. Several children who had seemed hopeless as far as training for cleanliness was concerned suddenly started to use the pot regularly. The intimacy of bathing time, she writes, has had a remarkable effect on the development of speech.

Kraus,[5] in an excellent paper, reported in 1954 his observations of what he calls his "total responsibility program" in a back ward building. He put his emphasis on careful grouping of the patients group activities and the delegation of some responsibility to the patients, letting them shave themselves, handle money and walk freely about the grounds. His was a pre open-hospital venture and he went about half-way in the direction taken by later and riskier experiments. He quotes no figures, saying only that many improvements were seen in his patients. Klemes,[6] reporting on the therapeutic effect of group morale in a psychiatric hospital in 1951, claims only that everyone was happier.

I believe it was the famous papers of Stanton and Swartz[7] in 1949 which opened the flood gates of the current tide of interest in sociological psychiatry. They showed conclusively how sensitive patients were to their environment and how easily they developed symptoms in response to conflicts in the persons responsible for their care. Harry Wilmer,[8] working in a Navy Hospital with the concept of the therapeutic community, as developed by Maxwell Jones in England, reports improvement in the morale and activity of his patients and emphasizes that tranquilizers introduced in quantity during his experiment did not do much beyond what management had already done.

In recent years there have been a few rather carefully worked out studies of this approach. Rashkis and Smarr[9] working at the Philadelphia State Hospital made a meticulous attempt to differentiate drug and milieu effects with chronic schizophrenics. Patients on their research unit were kept in a pre-drug phase for seven months before a variety of the new drugs were tried on them. They conclude that all of the change which they saw, and it was a significant one, was due to milieu effect. There was no significant change, they say, during the drug phase. In fairness, it should be stated that they selected very ill back ward patients who would presumably have a poor prognosis on drugs anyway. Clark and Hoy[10] in England in a careful study disclaimed cures or increased discharges on chronic patients through the use of the milieu approach except in places where the hospital had been static. They noted a limited improvement in morale and patient activity. The study gives a very good and detailed outline of the steps taken in their method. David Hamburg[11] at Michael Reese Hospital, in comparing 90 day periods in 1953, the pre-sociological period at the hospital, with 1955, reports that disturbances among the patients, resignations among the staff and definite improvement in the patients, all about doubled. Pace[2] reports a significant improvement by a milieu approach, though here he says nothing about the use of tranquilizers, weakening the validity of his results. He introduces

the term "learned incapacity" brought about in the patient by the hospital environment. Presumably he structures his approach so that the patient will "utilize capacity." The effects of changes of milieu on body chemistry were studied in the community of a metabolic ward by Schottstaedt, Stewart Wolf and others,[13] who find that changes in excretion of water, sodium, potassium, calcium, nitrogen and creatinine, showed fluctuations with milieu, demonstrating conclusively that we are dealing with a real force. The study by Galioni and Adams[14] from Stockton of the effects of increasing staff and activities in the patients is a very well known one and does show a significant positive change. Unfortunately their treatment more than doubled the per diem of cost of care to the patients.

I had a letter from Arthur Hecker, the Superintendent of Embreeville State Hospital, one of the few fully open hospitals in this country, telling me with figures what happened when he opened the doors. Unfortunately his figures show the effects of combined intensive milieu therapy and drug therapy. In the past three years his census dropped around 25% despite an increased patient intake of 230%. I am willing to believe that much of this effect can be attributed to the change in milieu, particularly since I have gone through his hospital and noticed that there is a considerable difference in the morale of the patients from that of patients in other closed hospitals where intensive drug therapy is used. But I cannot separate the results of the two kinds of treatments.

I have seen surprising effects from milieu therapy in an experience at Boston State Hospital. While my observations were not carried out long enough to constitute definitive proof, they were certainly suggestive enough to warrant my continued enthusiasm with these methods.

On taking over the male receiving in 1953 I found that the three wards were set up to receive incoming patients in rotation without regard to the patient's diagnosis or condition. Each ward had its own resident physician, a rather unusual arrangement designed to create family-like units presided over by a doctor, where the patient would feel that the ward was his home and from which he would not be transferred throughout his intensive treatment. He would come in on the ward and leave from the same ward. This arrangement appeared unsatisfactory to me for several reasons: timid schizophrenic patients were on the same ward with less inhibited psychopaths; shy patients who needed attention could not compete for it with those more adroit; the wards all needed considerable personnel coverage because each one had a few very difficult patients; the attendants were confused because of the variety of patients on the ward; there was no motivation in the scheme, since the patient had no way to be promoted or to be demoted—there was no way of indicating approval or disapproval; and there was no way, I thought, of opening the door on any of these wards. The setup, it seemed to me, could meet the needs of none of our patients. No *esprit de corps* developed on any ward. Accordingly I regrouped the service. One ward was for the court cases and the organic psychotics, another was for the timid ones who needed a great deal of attention, and another ward was open and inhabited by recovering patients. We could now re-assign and regroup the aides without adding to their number, in accordance with the ward needs and with the preference or ability of the individual aide.

The difficulties originally encountered seemed to have been largely solved by this regrouping. When we compared five-month periods under the same administration but two differing systems, we found that the turnover, calculating those patients released to the community over the number of admissions, had increased by 25%, an obvious and startling change. Transfers to the chronic wards went from the usual 25 or 30 during this five-month period down to two. In fact the Boston State Hospital census began to drop one year before the widespread use of tranquilizing drugs, most likely because of milieu therapy. Such unusually favorable results could not be expected to continue since there had been a backing up of those patients amenable to milieu therapy, and certainly milieu is not a panacea.

An approach such as the one reported from Boston State appeals to common sense

because it is based on careful attention to the needs of various kinds of people. I am uneasy about the open hospital concept which assumes that all patients will benefit from freedom. I have encountered patients who have been made anxious, who have considered premature freedom a form of rejection and I know of some who have attempted suicide and others who have committed aggressive acts because of their fears. However, the reports so far about the open hospital are universally favorable and the idea must, and no doubt will, be given a full-scale tryout.

The milieu approach once grasped opens the way to a host of new problems; such fruitfulness helps to justify a new idea. Milieu acts as a conditioning agent often in unintended ways, as Pace suggests by his phrase "learned incapacity" and as one may infer from intensive psychotherapy on persons who have been hospitalized. I have noticed marked difference in schizophrenic behavior and language and religious manifestations in the hospitals where I have worked or visited. For example, frequent references by patients to people sucking their blood may possibly be correlated with the milieu. In one hospital there was an interesting group of patients who in their symptomatology seemed to identify themselves with animals.

Quite probably milieu potentiates or obstructs the effects of other treatment; certainly results do vary from hospital to hospital, even on the same patients given identical treatment. Alexander and Rosen[15] have pointed out how organic treatments varied in effect on patients depending on their current psychological state, and similar studies will be done to correlate results with current prevailing sociological issues.

The oft-quoted statement that a hospital is but the lengthened shadow of its director needs documentation. It will be instructive to know just how the leader's unconscious affects an institution in all its ramifications. The preliminary reports on milieu therapy which have been mentioned, and many others also, suggest that psychiatry is falling heir to a vast body of information and techniques with the utmost therapeutic usefulness. Because of its non-optional nature the force inherent in milieu compels our attention and detailed study.

Cleveland Psychiatric Institute, Cleveland 9, Ohio.

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Appraisal of Drug Therapy

HARRY A. LABURT, M.D.

The value of ataractic drugs in psychiatric treatment has been definitely established and we see a mounting enthusiasm for their use. However, indiscriminate selections of the drugs for the relief of every-day tensions is unsound. Support for the therapy is given by those who have achieved favorable results and they seem to be in the majority. Nevertheless, there are conflicting reports which leave the impression that the last word has not yet been said. More clinical and laboratory research is needed with adequate controls for critical evaluation of the various drugs' usefulness and liabilities.

Over 125 drugs have been tested in the various institutions of the Department of Mental Hygiene during the past ten years and a good fund of knowledge as to their effectiveness and usefulness is available.

Some of the newer drugs used in psychiatric practice may be classified as follows:[1]

I. TRANQUILIZERS AND ATARACTICS (Major Tranquilizers for Psychomotor Agitation)

1. PHENOTHIAZINE DERIVATIVES

Chlorpromazine	(Thorazine)
Promazine	(Sparine)
Prochlorperazine	(Compazine)
Perphenazine	(Trilafon)
Promethazine	(Phenergan)
Mepazine	(Pacatal)

and others

2. RAUWOLFIA (Alkaloids)

Reserpine	(Serpasil)
Deserpidine	(Moderil)
Rescinnamine	(Harmonyl, Raunormine)

and others

3. DIPHENYL METHANE DERIVATIVES Minor Tranquilizers for Anxiety Tension States

Azacyclonol	(Frenquel)
Alpha benzhydrol hydrochloride	(Meratran)
Benactyzine	(Suavital)
Hydroxyzine	(Atarax)

4. PROPANEDIOL DICARBAMATE (Substituted Propanediols)

Meprobamates	(Miltown, Equanil) Considered to be hypnotics by some.
Phenaglycodol	(Ultran)

II. STIMULANTS (Anti-depressives)

Iproniazid	(Marsilid)
Methyl-Phenidyl-acetate hydrochloride	(Ritalin)
Amphetamines	(Dexedrine) (Benzedrine)

and others

III. HYPNOTICS AND SEDATIVES

Methylparafynol	(Dormison
Glutethimide	(Doriden)
Ethchlorvynol	(Placidyl)
Methyprylon	(Noludar)

and others

Manufacturers have developed and promoted so many new drugs that it is impossible to comment on all, but brief reference will be made to a few.

Of the many tranquilizers and ataractics *chlorpromazine-hydrochloride (Thorazine)* is perhaps the most widely used in hospitals. While it is effective there is considerable toxicity. It is most frequently given in states of aggression, confusion, hypermotility, maniacal states, anxiety and agitated depression.[2,3,4,5] Smaller doses control senile agitation.[6] Treated cases should be followed by psychotherapy. There are some side effects to be avoided. The World Health Organization recently added tranquilizers to their list of habit forming drugs. Jaundice is often noted. Tiny biliary thrombi are said to be responsible. Some cases clear up, while under medication. In others the medication must be reduced or stopped. This condition may occur in one to five per cent of treated cases. Blood dyscrasias are more serious where treatment is prolonged. It has been reported that leucopenia may occur in one-third of cases treated with chlorpromazine. Other complications may be agranulocytosis, eosinophilia and anemia. Additional side

Creedmoor State Hospital, Queens Village, L. I., N. Y.

effects are noted such as parkinsonism, allergies, depression, anorexia, weakness, dizziness, convulsions, etc. These drugs should not be used in patients with liver damage, extrapyramidal conditions, acutely ill with infectious diseases or with high doses of hypnotics and alcohol.

Promazine (chlorpromazine without the chlorine atom) Sparine, is weaker and less rapid in action but less toxic and produces fewer liver disturbances. Manic and paranoids do well on this drug.

Meprobamate (Miltown, Equanil) is used in anxiety and tension states. It assists in the control of alcohol withdrawal symptoms and does not interfere with use of Antabuse.[8,9] It is commonly used in office practice and, unfortunately, in great public favor with much self-medication amongst the laity.

Prochlorperazine (Compazine), a newer tranquilizer and antiemetic, analogue of chlorpromazine. It is less toxic and rapid in action. It is useful in mild, emotionally disturbed or ambulatory mental cases and those with various somatic complaints. If used for short periods, 10 days to two weeks, side effects are minimal. It can be used for much longer periods with relative safety. Contra-indicated in markedly depressed or comatose states due to use of CNS depressants.[10,11] However, the drug must be used cautiously as symptoms of retinitis pigmentosa may develop.

Reserpine (Serpasil, Serpiloid, Rau-Sed., Sandril) is a disappointment to many while others consider it valuable. It has calmed hospitalized patients resulting in quieter wards, allowing more constructive uses for personnel time. Patients eat and sleep better, recover more rapidly. It relieves tension, anxiety, restlessness, excitement, assaultiveness and destructiveness. It is effective in arteriosclerotics and seniles, paresis and delirium tremens. Severe side effects have been reported, i.e., Parkinson-like symptoms, sudden respiratory arrest, cardiovascular collapse, peptic ulcer formation, gastrointestinal hemorrhage, diarrhea, urinary symptoms, increased convulsions in epileptics and severe depressions.[12,13,14] This drug should not be used in depression without agitation, disorders without emotional disturbances, edematous patients, or patients with alimentary tract lesions. It may be used as a maintenance treatment in place of ECT in assaultive and overactive patients, but it cannot replace ECT or ICT in acute cases.[15,16]

Ritalin is the most common of the CNS stimulants. It has little or no effect on blood pressure, blood sugar, blood count or urinary function. It produces mild stimulation without euphoria and no tachycardia. In depressed patients it produces favorable results with improved appetite and circulation. It is equivocal in chronic schizophrenics. It may stimulate those patients who are too drowsy with use of other drugs, or those who are retarded or inert.

Iproniazid (Marsilid), a monoaminoacid oxidase inhibitor is a potent anti-depressant. Due to its toxicity it received unfavorable publicity and its use has been greatly curtailed.

Metrazol—a stimulant—is used in seniles and arteriosclerotic to reduce hypertension, elevate mood, reduce fatigue and modify social behavior.[17,18] However, reports as to its value are not conclusive.

In the field of hypnotics and sedatives, there are many who prescribe the newer drugs listed above, but there are still those who prefer the older barbiturate sedatives. Phenobarbital 120 mg. daily has been found as effective as chlorpromazine 100 mg. daily or Serpasil 2 mg. daily in a month's trial of newly admitted patients.[19]

Many use Pentobarbital with satisfactory results despite hangover subsequent to its use.[20]

Although some interest had already been aroused in psychotropic drugs prior to December 1954, full-scale use of these drugs was instituted on the above date. The drugs available at that time were mainly those of the phenothiazine group and the reserpines. Of these, the more popular were Serpasil and Thorazine. The main use of these drugs were indicated as being for the control of anxiety and agitation. A large number (approximately 25%) of the patient population in the hospital were placed on these drugs. The effect was rather dramatic almost im-

mediately. The agitation and anxiety noted previously was promptly brought under control. The general hubbub which was previously an intrinsic part of disturbed wards and reception services diminished. The patients on these wards became more amenable to individual and group therapy, as well as the other ancillary activities such as recreational, occupational, and educational therapies. The atmosphere of the hospital and its wards improved, permitting personnel to embellish the appearance of the wards, permitting the maintenance staff to decorate in brighter colors, and permitting the clothing of the patients to be more in keeping with the general population than that of institutional inmates. As the program grew, it was noted that for the first time the census of the institution began to reduce. Whereas previously there was an increase in the hospital census each year, now the trend was reversed. Considering the continued increase in the total number of admissions each year, the reduction assumed more weight as time progressed. The need for individual and group therapies became more apparent. Inter-personal relationships between patients improved. Many who were considered permanent residents on the "back wards" began to take an interest in their surroundings, request interviews, seek permission to enter into activities, and finally some sought release from the hospital. The need for shock treatment, especially in control of behavior, became less. Their attitudes became more cheerful and alert.

As the program progressed and with the advent of the meprobamates (Miltown, Equanil) and the prochlorpromazines (Compazine) fears instilled by the side effects of the reserpines and the phenathiazines were overcome and increased therapy could be undertaken. The need for acute shock therapy diminished. Residence in the hospital setting became less. The discharge rate increased. At first it was felt that perhaps some changes in trends of admission and certification might have been responsible for this increase in discharge rate. However, close examination of the statistics indicated that in reality the numbers of those released from the hospital increased in total. The convalescence rate remained about the same. The return rate from convalescence diminished as these patients were permitted to be followed in aftercare clinics, many still using the ataraxics. With all these changes came a need for organizational change within the hospital itself. More concentration of personnel in all modalities was found necessary. Early treatment became more and more indicated and more and more vital. Whereas previously the time of evaluation was necessarily longer because of the inability to communicate directly and to establish inter-personal relations with the patient, now it was noted that evaluation had to be thorough but rapid. Therapy began even before total evaluation had been completed. The need for restraint and seclusion diminished to practically none at all. Group therapy began to increase as more and more patients became amenable to this type of aid. Occupational and recreational therapy showed marked upsurge in attendance. The occupational and recreational therapists found it easier to assume greater case loads because of the calmer behavior of the patients.

Most recently, extension of an open ward policy became feasible because of the improvement of attitudes of patients and compliance with the regulations. Patients began to show ability to assume responsibility and to reinstitute their individuality with personal integrity being improved and maintained to a high degree.

The most startling factor of the psychotropic drug therapy has been the diminution of hospital time necessary in the majority of cases. Whereas previously we thought in terms of six months to a year, now we consider one or two months as hospital time. The clinical division of the hospital began to assume a heavier proportion of responsibility in the function of the hospital. The emphasis for therapy necessitated the establishment of an intensive and extensive residency training program. No longer were psychiatrists faced with the chore of continued treatment notes, but rather found themselves faced with the need for giving dynamic psychotherapy.

A large mental institution now finds itself in a peculiar situation of being almost the entrepreneur in mental illness. The general practitioner, mental hygiene clinics, and pri-

vate practicing psychiatrists are able to keep their patients ambulant longer, even to the point of circumventing hospital treatment in its entirety. The aftercare clinics, general practitioners, and private practicing psychiatrists are able to reassume the responsibility for their patients at an earlier date and to be able to care for them with safety and equanimity in the community. Indeed, the large mental institution now finds itself in the position of the general hospital with regard to mental illness. It cares for the acute conditions and major psychiatric syndromes and delegates pre-hospital care and the convalescence to community services.

Of course, in the consideration of the aging population and in the deteriorating psychoses incident to arteriosclerosis and senility, the outlook is not as encouraging. Even in these cases, attitudes in the hospital have improved with the use of drugs. These patients are being handled with greater ease. Even in these categories an increase in the release rate has been noted.

Should the present course of the large mental institution continue in the same pattern that has been established during the past five years, it is felt that the mental institution will be for the acutely psychotic and for the elderly who show no improvement with intensive therapy. This will not diminish the need nor the requirements of the large mental institution. Indeed, it may even expand the necessary function because of the vital concentration as has been noted previously. The atmosphere will change, not only insofar as to the atmosphere of the wards, but also as it concerns the patients themselves and the psychiatrists. Training will be vital. Alert, dynamic approach to psychiatric illness will be essential. The challenge is one which will have to be met at all levels and in all categories.[21]

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CO_2 Therapy in Broad Spectrum Psychiatric Treatment

PAUL H. WILCOX, M.D.

This three day program of the Eastern Psychiatric Research Association is a splendid example of what I have chosen to call "broad spectrum psychiatric treatment." One of the basic principles of ethics of general medical practice is that the physician should not be a cultist—that he should be broadly eclectic in his choice of methodology, drawing from every possible area in order to give the appropriate treatment to any specific patient.

Ever since Dr. Meduna introduced CO_2 therapy in 1945 as a treatment for psychoneuroses, CO_2 therapy has been a controversial subject. There have been those who at one time or another have recommended that the general practitioner be trained in the use of CO_2 therapy with the expectation that he could use it treating selected psychoneurotics in his general practice. In contrast there have been bans in various state and veterans' hospitals against its use at all.

Furthermore, there has been wide divergence in the ranks of those who have used CO_2 therapy as to how it should be used. I shall not attempt to give the pros and cons of the various CO_2 methods in this paper. I have chosen, instead, to describe my own present usage of CO_2 in private office psychiatric practice after having used it for 12 years.[1]

In the first place I wish to divide broad spectrum psychiatric treatment into the following subdivisions:

1. Convulsive electrostimulation
2. Non-convulsive electrostimulation
3. Non-coma CO_2
4. Coma CO_2
5. Coma insulin therapy
6. Subcoma insulin therapy
7. Drug therapy
8. Psychotherapy

I have not attempted to use either coma or subcoma insulin therapy in my private office practice and my use of drug therapy has been minimal, mainly supportive, while I carried out what I have felt were more definitive procedures. I have felt that all my psychiatric procedures should be appropriately infiltrated with psychotherapy, but I treat only a few of my patients with psychotherapy alone. This leaves my area of primary discussion to be centered around convulsive electrostimulation (ECT), non-convulsive electrostimulation (ESnc), non-coma CO_2 (CDTnc) and coma CO_2 (CDT). ESnc and the CDT's can be considered facilitative or abreactive therapies, whereas ECT is primarily a sedative-repressive therapy.

Abreactive therapy tends to be dramatic and there is a temptation to measure its value in terms of the degree of abreaction obtained in a given session. However, I was disillusioned on this point after having certain patients repeatedly react in a spectacular way without showing improvement and in some cases even with worsening symptoms. These observations led me to devise a psychiatric rating scale[7] in order to help to analyze which clinical symptoms responded favorably and which unfavorably. It became apparent to me that the main hazard of ESnc and CDT was their tendency to increase suicidal risk in patients having endogenous depression. However, I found myself defining an endogenous depression as follows: An endogenous depression is one which tends to be aggravated by ESnc and by CDT but tends to be relieved by ECT. Contrariwise, I define a reactive depression as one which tends to be relieved by ESnc and by CDT but tends to be aggravated by ECT. This pattern of classification has not been generally accepted, but I contend that when the treatment tests have been followed through according to my outline, more people will see the evidence in favor of my claim.

My first concern when seeing a patient is whether he is a serious suicidal risk. With this in mind, I do not think it is wise to treat any patient with either ESnc or CDT unless you also have the facilities for giving ECT if and when the indications develop. This concept would make it undesirable for a general practitioner to fool around with CDT.

Dr. Paul Wilcox, for this paper, was awarded a prize of $100.00 by the Institute of Psychiatric Treatment, Boston, Massachusetts for the best contribulation read during the first day of the meeting.

At this point I would like to quote the summary of my 1954 paper on, "Coordination of Electrostimulation with other Techniques in the Treatment of Neurotic Symptoms."[7]

"In neurotic patients whose psychosomatic symptoms and/or depression are accompanied by relatively mild anxiety, intensive psychotherapy facilitated by non-coma and coma CO_2 treatments usually produces efficient results. However, in the presence of certain specific symptoms, such as: various organic changes, systolic B.P. over 170 mm. Hg., marked fear and anxiety, severe nightmares, agitation, sleeplessness, obsessive-compulsive features, severe guilt feelings, marked hate and aggressive tendencies, marked irritability, feelings of unreality, feelings of confusion, and paranoid trends, non-convulsive electrostimulation under sodium pentothal anesthesia is the treatment of first choice. In such cases CO_2 treatments may then be used in the later stages of their treatment where indicated."

In my chapter on "Selective Use of Carbon Dioxide as an Aid to Psychopenetration" in the 1958 edition of the book edited by Dr. Meduna, *Carbon Dioxide Therapy,*[8] I presented seven case studies, namely:

1. "Normal" Case.
2. Case of Mild Anxiety and Depression.
3. Case of Psychosomatic Symptoms with Associated Depression.
4. Case of Petit Mal Epilepsy with Disturbance of Body Image, Acute Anxiety and Moderate Depression.
5. Case of Anxiety and Depression with Alcoholism and Paranoid Trends.
6. Case of Bizarre Somatic Complaints with Moderate Anxiety and Depression.
7. Case of Acute Anxiety Attacks with Strong Resentment and Mild Paranoid Trends.

Of these cases the first four were presented as illustrations of the successful use of CDT as a part of the therapy. The fifth and sixth were presented to illustrate how the CDT failed to prevent a paranoid breakdown and a hallucinatory breakdown, respectively. The seventh case was successful in spite of paranoid trends but in the light of subsequent experience it was thought probable that his progress would have been more rapid if a series of ESnc's had preceded the CDT's.

In my paper entitled, "A Score Sheet for Analyzing the Indications for Electroconvulsive Treatment in Office Psychiatric Practice,"[9] which was presented at the 1957 Electroshock Research Association Meeting, I referred to two patients who committed suicide who had had CDT as part of their therapy. I wish to present these two cases in more detail at this time to show that CDT did not prevent suicide in those cases and may even have increased the hazard. If a patient receiving CDT shows mounting apprehension or shows an increase of depression either during the therapy hour or during the next few days, it is wise to switch the treatment promptly to ECT's.

Case M. C. This patient was a white widow aged 52. She showed severe depression, retardation, agitation, and sleeplessness and she was free from schizoid trends. Today, I would insist that she be hospitalized for treatment and would start her on ECT's. In 1952 when she was my patient, I let her and her relatives talk me into trying to treat her in the office. I decided to try her on ESnc because it was a milder treatment than ECT. There was an increase in depression in the course of six treatments. Still wanting to try out the milder treatments, I changed to CDT. Her reaction to the CDT was relatively mild which is not unusual with endogenous depressions. The next day she reported that she felt better. On that day she was given another CDT. This precipitated a grimacing, struggling, clawing pattern during the sleep phase. On awakening, she recalled a dream in which she was almost struck by an automobile as she was crossing a street and she was running to avoid the auto. She claimed to be feeling good at the end of the hour and her mind seemed clear, though she still felt somewhat jittery. Five days later she committed suicide by drowning. In retrospect it appears to me that the adverse reactions to ESnc indicated the need for ECT and that the favorable response to CDT in an agitated depression was spurious.

Case H. R. This middle-aged man also presented severe agitation. After three ECT's he had apparently shown considerable improvement, and the agitation also had subsided. Thus encouraged, I switched him to ESnc with a seemingly favorable response except that some agitation returned. An attempt was made to treat this component with CDT. His symptoms were getting worse so after nine CDT's he was changed back to ESnc. A couple of days later he committed suicide. In retrospect it seems that the return of agitation with the ESnc should have warned me to return to ECT rather than try the CDT.

These two cases indicate that CDT did not prevent suicide even when the immediate response seemed favorable.

Now I would like to present a case of a mild catatonic boy of 19 in whom irritability as a complication of ECT's was dramatically improved by CDT's as the final phase of therapy.

Case V. T. This single white male aged 19 admitted severe depression but did not have significant retardation, agitation or sleeplessness. He had feelings of depersonalization, unreality and ideas of reference but he denied ideas of persecution. Because of his suicidal preoccupation and his catatonic appearance ECT was chosen for the initial treatment. After 19 ECT's his depression scores and his schizoid freedom scores were still the same, but irritability at home was increasing. One ESnc was tried but the response was unfavorable because depression increased before the end of the hour and in the subsequent two days. Two days after the ESnc he was started back on ECT's which counteracted the extra depression but the irritability at home continued to be a problem. There were still suicidal thoughts but not as pressing as for the two days after the ESnc. However, in spite of these symptoms, an important change had taken place. He had become flexible to some of my psychopenetration questions and the general impression was that he was more accessible and less stereotyped. He was therefore tried on CDT. His response was immediately favorable without apprehension or increase of depression. After six sessions of CDT in the course of three months, he was free from depression and his feelings of depersonalization, unreality and reference had cleared up. It has now been over two years since his last treatment and he is still making a very good adjustment at home and at work.

Now I would like to review the history of some of my thinking. When I first talked to Dr. Meduna in 1946 about CO_2, it appealed to me as a possible short-cut method of psychoanalysis, because of the dream production almost on demand. For two years, I followed the assumption that CO_2 dreams could presumably be analyzed pretty much in Freudian terms and with that in mind I tried to find hidden sex meanings whenever the dreams were obscure. However, in 1948 I had a patient who had numerous, varied and bizarre CO_2 sex dreams and who showed no clinical improvement in spite of hours of discussion. Finally, a set of circumstances led me to wonder whether these dreams were being motivated by a wish for attention. When this approach was made the dreams rapidly changed their character and clinical improvement began. This observation strengthened my impression that CO_2 dreams tend to repeat but when they are adequately interpreted, they tend to change or diminish. It appeared that parts of CO_2 dreams could be subtracted by appropriate analysis. This resulted either in a diminution of the dream response or a replacement by some other theme apparently emerging from a slightly deeper layer of the unconscious. This discovery, that analysis of this patient's dreams in terms of a wish for attention was more effective than analysis in terms of sex, opened the door for a new scheme of analysis. In the subsequent months, a whole series of taboo words were found to be symbolized in CO_2 dreams. Out of these findings I coined the word psychopenetration which I have defined as any process which causes changes in the unconscious mind which can be corroborated by a message back from the unconscious mind. I therefore described psychopenetration as cybernetic treatment of the unconscious. I selected seven questions which I called the psychopenetration test. These questions were published in 1951[5] and are as follows:

1. Do you unconsciously believe you *own* everybody and everything all the time?
2. Do you unconsciously want *attention* from everybody all the time?
3. Do you unconsciously have *sexual feelings* towards everybody and everything all the time?
4. Do you unconsciously want to *kill* everybody and everything all the time?
5. Do you unconsciously want to *submit* to everybody in every way all the time?
6. Do you unconsciously want to *show all* your *feelings* to everybody all the time?
7. Do you unconsciously want to *deceive* everybody all the time?

Misconceptions have arisen about this test because some have tried to use the questions as a therapy by themselves. The test is whether after suitable explanations[6] an individual can see the possibility of the answers to these questions being "yes" for the unconscious mind in spite of their being "no" for the conscious mind. It was found that most established schizophrenics were unable to see through these explanations.[3] A parallel observation was that such patients failed to get any benefit from CDT no matter how vivid the reactions and no matter how persistent I was in trying to help them understand the experience. On the other hand, psychoneurotics as a group were flexible to the questions and tended to be benefited by CDT. As time went on I found that certain psychoneurotics with schizoid components tended to overreact to the CDT so that it

was difficult to get their cooperation in continuation of the therapy. For these, ESnc tended to be especially beneficial. Two groups of patients who tend to be flexible to the questions fail to benefit from CDT, namely, endogenous depressions and psychopathic personalities.

Thus, of those who proved flexible to the questions, the patients who responded well to CDT narrowed down to those neurotic patients whose psychosomatic symptoms and/or depression are accompanied by relatively mild anxiety, ruling out schizophrenics, endogenous depressions, psychopaths, and neurotics with prominent schizoid trends. However, CDT has been useful during the final phase of treatment in schizophrenics and schizoid neurotics when their major symptoms have subsided and psychodynamic insight is desired.[2]

The psychopenetration questions, when integrated in the therapy of suitable patients, prove very useful as building blocks of psychodynamic insight into the operations of the unconscious mind.

In 1950 I ran into a complication with a young woman when CDT precipitated in her a gross incapacitating shaking which had the characteristics of hysteria major. I had the privilege of having Dr. Meduna see her in consultation in Chicago. We hesitated to pursue the CDT, so he recommended hypnosis as a correcting therapy. One of my colleagues undertook this approach and after about 18 hours of practice the patient was induced into a moderate degree of therapeutic hypnosis and her symptoms began to subside.

In the meantime, I had been intensely concerned with finding a way to anticipate such a major reaction from CO_2 and perhaps prevent it. One day when I had given a patient a few sample whiffs of 20% CO_2-80% O_2, I asked her a differently worded question than I had previously. My question previously had been, "What does it make you think of?" but this time I asked, "What sensations do you notice?" Her answer included a variety of sensations which I had not experienced myself when testing samples, so I began to systematically ask my patients the new question. Thus I discovered that the reaction to whiffs of mixtures of CO_2 and O_2 produced different reactions in different people. These reactions tended to repeat on successive samples until appropriately analyzed and then the reaction would diminish or entirely disappear! This then added significantly to my psychopenetration procedure.

I then returned to my hysteria patient who was now much improved and gave her a few whiffs of the 20% CO_2 and 80% O_2 mixture and I was able to elicit temporary trace reactions of the shaking without precipitating the major tremor. Then I began trial and error analyzing and finally came up with the formula that "shaky" represents the unconscious wish to submit and run away at the same time. When this pattern was discussed in relation to her mother, flashes of insight and vivid childhood memories were recalled. Then the CO_2-O_2 whiffs failed to precipitate the tremor. Gradually we increased the dosage and she still remained free of the tremor. A report some years later indicated that she had remained symptom free except for a few weeks later in that first year.

On the basis of this new chain of observations, my present policy is to work through the reactions to gradually increasing non-coma doses of CO_2 before putting the patient to sleep. If there are any signs of over-reaction, I avoid putting the patient to sleep with the CO_2 until the reactions have become mild. Often such over-reactions are indicative that better progress will be made with ESnc.

My use of CO_2 in appropriate selected cases has been a most fascinating and rewarding therapy. A great deal has depended on my creative imagination during the session. If I am overtired at the time my efficiency in discovering the interpretations that result in a diminution of the CO_2 reactions drops off sharply.

Theoretical Considerations

Probably the unconscious mind functions by means of innumerable reverberating circuits with multiple registration, linking all parts of the brain approximately as extensively as is credited to the conscious mind. Whatever the actual neuronal basis may be, the unconscious mind seems to be organized

in functional layers or compartments which have various boundaries separating the layers from one another and from the conscious mind or Ego. Additional functional lines of cleavage within the Ego and within the unconscious mind may occur as pathological dissociation in various degrees. These boundaries are not solid barriers but rather act as differential filters allowing some forces to emerge more than others.

Both CDT and ESnc tend to bring to the surface endogenous depression, whereas generalized convulsions (e.g., ECT) tend to counteract endogenous depression. In my 1946 paper, "Brain Facilitation Not Brain Destruction, the Aim in Electroshock Therapy,"[10] I postulated that the convulsion somehow produces "a facilitation of the integrative brain patterns previously inhibited by the pathological process" of an endogenous depression. Along this line of reasoning, it would seem that CDT and ESnc increase the inhibition of some of the integrative brain patterns but in different ways which result in various patterns of *transient dissociation.* These transient dissociation patterns tend to increase the kind of intrinsic dissociation in the endogenous depression. However, in a reactive depression the innate restorative potentiality of the person is more adequate so that the dissociation stimuli provoke the restorative integrative forces on the basis of a higher control system which we often call "insight" and the reactive depression is corrected. My patient with hysteria major was susceptible to a pattern more commonly recognized as one of severe dissociation. Her "insight" control system became adequate when small doses of CDT (a sort of desensitization) were used, whereas her illness was aggravated by large doses of CDT (a sort of anaphylactic shock phenomenon).

Summary

Carbon dioxide therapy (CDT) has an important place in office psychiatric treatment of mild psychoneurotics, but it must be used with discrimination or adverse reactions and wasted efforts result. CDT should not be used unless the physician also has facilities for giving ECT because CDT can bring out a latent endogenous depression which may lead to suicide if the warnings are overlooked and appropriate supervision and ECT treatment are not instituted. Non-coma carbon dioxide treatments (CDTnc) are useful in clearing repressed material from the upper layers of the unconscious mind so that coma treatments result in less violent reactions. CDT is an abreactive therapy which is mainly useful as an adjunct to intensive psychotherapy of a type which I call psychopenetration. CDT is dangerous in endogenous depressions, may cause the patient to prematurely interrupt therapy if over-reactions are permitted, and is futile in the treatment of established schizophrenics and psychopaths. It sometimes is useful in the final reconstruction phase of the successful treatment of schizophrenics and of severe schizoid neurotics. Theories regarding dissociation were discussed.

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526 W. 10th St., Traverse City, Mich.

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Care and Treatment of the Senile and Arteriosclerotic Mental Patient

NATHAN BECKENSTEIN, M.D.

With increasing life expectancy there has been a corresponding increase in admissions of patients suffering from the psychoses of the senium, mainly senile psychoses and psychoses with cerebral arteriosclerosis.

TABLE 1

*Life Expectancy Table—U.S.**

	Whites			Non-Whites			All Races		
Year	Both Sexes	M	F	Both Sexes	M	F	M	F	Both Sexes
1900	47.6	46.6	48.7	33.0	32.5	33.5	46.3	48.3	47.3
1927	62.0	60.5	63.9	48.2	47.6	48.9	59.0	62.1	60.4
1955	70.2	67.3	73.6	63.2	61.2	65.9	66.7	72.9	69.5

*Statistical abstract of the United States, 1957. 78th Edition, Bureau of the Census, U.S. Dept. of Commerce, page 60.

Life expectancy for both sexes has risen from 47.3 years in 1900 to 69.5 years in 1955 (Table 1). Women live longer than men, and whites longer than non-whites.

TABLE 2

Psychoses of the Senium—First Admissions

	New York State Hospitals	Brooklyn State Hospital
1943	10,935	1,492
Senile (%)	8.6	16.8
Psychosis w. CAS (%)	16.6	19.0
Total (%)	25.4	35.8
1957	19,951	1,063
Senile (%)	16.2	34.0
Psychosis w. CAS (%	23.9	28.0
Total (%)	40.1	62.0

In 1933 (Table 2) psychoses of the senium accounted for 25.4 per cent of the first admissions to New York State mental hospitals. (8.6% senile and 16.6% cerebral arteriosclerotic psychotics.) At Brooklyn State Hospital that year they accounted for 35.8 per cent of the first admissions (16.8% senile and 19.0% cerebral arteriosclerosis).

From Brooklyn State Hospital, Brooklyn, N. Y.

In 1956, the latest published statistics, the statewide first admissions showed 40.1% psychoses of the senium (16.2% senile and 23.9% psychosis with cerebral arteriosclerosis). At Brooklyn State Hospital psychoses of the senium rose to 62% (34% senile and 28% psychosis with cerebral arteriosclerosis). Brooklyn State Hospital is adjacent to Kings County Hospital Observation Ward and thus admits many patients who are too feeble to travel longer distances to a more distant hospital.

In 1945 we compiled a study of 200 consecutive first admissions made in 1943 of patients with psychoses of the senium. At that time we did not have widespread use of the antibiotics, there were few community programs for the aged; we had no tranquilizing drugs, and a social security program was not yet in full operation. We compared this study with a study on 200 patients admitted to Brooklyn State Hospital in 1957 who had better health programs, day center care, and greater social security benefits. We chose for our study 100 consecutive first admissions of patients with senile psychoses and 100 consecutive admissions of patients with cerebral arteriosclerosis between January and April 1957. This latter study was begun September 1, 1958.

TABLE 3

Age Distribution—Senile Psychoses

	Dead			In Hosp.			Out of Hosp.			Total		
Age	M	F	T	M	F	T	M	F	T	M	F	T
61-65	0	1	1	0	0	0	0	0	0	0	1	1
66-70	1	0	1	0	4	4	0	0	0	1	4	5
71-75	3	12	15	0	4	4	1	4	5	4	20	24
76-80	8	4	22	3	3	6	0	0	0	11	17	28
81-85	6	7	13	1	6	7	0	1	1	7	14	21
86-90	1	8	9	0	2	2	0	1	1	1	11	12
Over 90*	4	5	9	0	0	0	0	0	0	4	5	9
Total	23	47	70	4	19	23	1	6	7	28	72	100

*Two patients 100 and 101 years old.

Table 3 shows that 70% of our senile patients were over 76 years of age, as compared with 66% in that category in 1943. In the present study the two oldest patients

were 100 and 101 years. In the 1943 series the oldest was 92 years.

TABLE 4

Age Distribution—Psychosis With Cerebral Arteriosclerosis

Age	Dead			In Hosp.			Out of Hosp.			Total		
	M	F	T	M	F	T	M	F	T	M	F	T
Under 50	0	0	0	0	1	1	0	1	1	0	2	2
51-55	2	0	2	2	2	4	1	0	1	5	2	7
55-60	1	1	2	0	2	2	0	0	0	1	3	4
61-65	3	3	6	0	2	2	1	1	2	4	6	10
66-70	4	10	14	0	6	6	2	4	6	6	20	26
71-75	3	7	10	2	4	6	2	0	2	7	11	18
Over 76	11	10	21	3	4	7	4	1	5	18	15	33
Total	24	31	55	7	21	28	10	7	17	41	59	100

Table 4 demonstrates the situation with the cerberal arteriosclerotic, 49% were under 70 years of age as compared with 68% in 1943, 23% were under 65 as compared with 47% in 1943.

TABLE 5

Duration of Hospital Residence—Senile Psychoses

Age	Dead			In Hosp.			Out of Hosp.			Total		
	M	F	T	M	F	T	M	F	T	M	F	T
Under 1 week	6	1	7	0	0	0	0	0	0	6	1	7
1-2 wks.	2	4	6	0	0	0	0	2	2	2	6	8
2-3 wks.	1	3	4	0	0	0	0	2	2	1	5	6
3-4 wks.	4	9	13	0	0	0	0	0	0	4	9	13
1-2 mos.	0	12	12	0	0	0	1	1	2	1	13	14
2-3 mos.	1	5	6	0	0	0	0	0	0	1	5	6
3-6 mos.	5	7	12	0	0	0	0	0	0	5	7	12
6 mos.-1 yr.	2	3	5	0	0	0	0	1	1	2	4	6
1-2 yrs.	2	3	5	4	19	23	0	0	0	6	22	28
Total	23	47	70	4	19	23	1	6	7	28	72	100

Further analysis of the tables indicates that 70 seniles and 55 cerebral arteriosclerotics, a total of 125 died in the hospital in the 1957 groups, and a total of 148 in the 1943 study. Fewer patients died in the present series. Interesting also is the fact that while more remained alive in this study, the same number, 24, of the 200 cases in both studies left the hospital; 51 in this study remained in the hospital, 28 in 1943.

Duration of Hospital Residence

Table 5 lists time in the hospital. Among the senile deaths 48 (68.5%) died within 3 months; 60 (85.7%) within 6 months, and 30 (42.8%) within 1 month. In 1943, 63.2% died within 3 months; 91% within 6 months, and 47% within one month.

TABLE 6

Duration of Hospital Residence—Psychosis With CAS

Age	Dead			In Hosp.			Out of Hosp.			Total		
	M	F	T	M	F	T	M	F	T	M	F	T
Less than 1 week	0	1	1	0	0	0	2	0	2	2	1	3
1-2 wks.	3	2	5	0	0	0	1	1	2	4	3	7
2-3 wks.	1	1	2	0	0	0	0	1	1	1	2	3
3-4 wks.	3	11	14	0	0	0	0	1	1	3	12	15
1-2 mos.	5	3	8	0	0	0	1	1	2	6	4	10
2-3 mos.	5	5	10	0	0	0	1	2	3	6	7	13
3-6 mos.	6	4	10	0	0	0	3	1	4	9	5	14
6 mos-1 y	0	2	2	1	1	2	2	0	2	3	3	6
1-2 yrs.	1	2	3	6	20	26	0	0	0	7	22	29
Total	24	31	55	7	21	28	10	7	17	41	59	100

Table 6 lists those in the arteriosclerotic group who died; 40 (72.7%) died within 3 months; 50 (90%) within 6 months, 22 (40%) within 1 month. In 1943, 68.8% died within 3 months; 78.6 per cent within 6 months, and 45.9% within 1 month.

Taking both conditions together, 70% died within 3 months, as compared to 52% in 1943; 88% within 6 months as compared to 78%, and 41.6% within 1 month as compared to 46.6%. In both studies there was only a slight difference in the percentage dying within one month. When 6 months passed, however, a greater percentage died in the 1957 series. It is probable that, besides their older age, they may have had severer debilitating conditions.

Duration of Symptoms Prior to Admission

It is important to know how long mental symptoms were present before the patient came to the hospital. Was there any difference in duration in the patients who died and in the patients who remained alive. It was not easy to get such information in all cases and in some the information was not forthcoming at all.

Table 7 lists the senile patients in whom information as to duration of symptoms prior to admission could be elicited: Of 59 deaths, 31 (52.5%) had symptoms over 2 years, as compared to 21.6% in 1943 study. Of the 21 in hospital, all 21, 100%, had symptoms under 2 years, as compared to 60 per cent in 1943. Of the 87 senile patients in whom duration of symptoms prior to admission was known, 59.7% had symptoms for less than 2 years, as compared to 77%

TABLE 7

Duration of Symptoms Before Admission—Senile Psychoses

Age	Dead			In Hosp.			Out of Hosp.			Total		
	M	F	T	M	F	T	M	F	T	M	F	T
Less than												
3 mos.	2	5	7	1	2	3	1	0	1	4	7	11
3-6 mos.	0	2	2	0	0	0	0	0	0	0	2	2
6 mos.-1 yr.	2	6	8	1	2	3	0	1	1	3	9	12
1-2 yrs.	5	6	11	1	14	15	0	1	1	6	21	27
2-3 yrs.	0	5	5	0	0	0	0	3	3	0	8	8
3-4 yrs.	1	5	6	0	0	0	0	0	0	1	5	6
4-5 yrs.	1	6	7	0	0	0	0	0	0	1	6	7
Over 5 yrs.	5	8	13	0	0	0	0	1	1	5	9	14
Unknown	7	4	11	1	1	2	0	0	0	8	5	13
Total	23	47	70	4	19	23	1	6	7	28	72	100

in 1943. These figures indicate that more patients were sick longer before admission in the 1957 series than in those studied in 1943. Both studies, however, show that the duration of symptoms prior to admission among the deaths was longer than that among those who remained alive.

TABLE 8

Duration of Symptoms Before Admission—Psychosis with CAS

Age	Dead			In Hosp.			Out of Hosp.			Total		
	M	F	T	M	F	T	M	F	T	M	F	T
Less than												
3 mos.	2	12	14	0	7	7	2	2	4	4	21	25
3-6 mos.	5	1	6	0	2	2	1	0	1	6	3	9
6 mo.-1 y.	6	6	12	1	3	4	0	0	0	7	9	16
1-2 yrs.	3	7	10	2	5	7	3	1	4	8	13	21
2-3 yrs.	1	1	2	2	1	3	1	1	2	4	3	7
3-4 yrs.	0	1	1	0	0	0	0	0	0	0	1	1
4-5 yrs.	2	0	2	2	0	2	0	0	0	4	0	4
Ov. 5 yrs.	3	0	3	0	2	2	0	3	3	3	5	8
Unkno'n	2	3	5	0	1	1	3	0	3	5	4	9
Total	24	31	55	7	21	28	10	7	17	41	59	100

Table 8 shows the situation among the arteriosclerotic patients. Of the 50 deaths in whom duration of symptoms was known, 8, or 16%, had symptoms over 2 years, as compared to 14.7% in 1943; 42, or 84%, had symptoms under 2 years, as compared to 85.3%; 32, or 64%, had symptoms under 1 year, as compared to 68.8% in 1943. Among the 27 patients in the hospital, 20, or 74% had symptoms under 2 years prior to admission, as compared to 77% in 1943; 13, or 48.1% under 1 year, as compared to 55%. Of the 14 who left the hospital 9, or 62.8% were sick under 2 years prior to admission, as compared to 95% in 1943, 5, or 35% under 1 year as compared to 85% in 1943. Of the 91 patients of known duration before admission, 71, or 78% were under 2 years, as compared to 86% in 1943; 50 or 54.9% under 1 year, as compared to 70%; and 25, or 27.4% under 3 months as compared to 27% in 1943. Among the patients suffering from psychosis with cerebral arteriosclerosis, the differences in the two studies were not significant except among those who left the hospital. In both studies, however, the duration of symptoms prior to admission in the arteriosclerotic was markedly shorter than in the senile patient.

TABLE 9

Strokes—Psychosis With CAS

	Dead	In Hospital	Out of Hospital
1 stroke	16	9	0
2 strokes	3	0	0
3 or more strokes	2	1	0
Total	21	10	0

Among the senile patients there was only 1 stroke. In the 1943 series theret were 36 strokes.

Table 9 demonstrates the picture of "strokes" recorded in the histories of the present study. Families will remember this physical condition because it is so dramatic and so often is accompanied by paralysis of a limb. In this series, 31 patients of the 200 gave a history of "strokes," 25 had one stroke, 3 had 2 strokes, and 2 had 3 or more strokes. In the 1943 study, 36 patients had a history of strokes.

TABLE 10

Reasons for Admission—Senile Psychoses

	M	F	T
Turned on gas and forgot to light it	1	3	4
Unable to care for patient at home (confused, disturbed, wanders, yells at night, etc.)	18	42	60
Unmanageable in other institutions (general hospital, nursing home, old age home)	4	10	14
Suicidal attempt	2	2	4
Unable to care for self	1	11	12
Accident	1	0	1
Advice of psychiatrist	0	1	1
Found in street hemiplegia	1	0	1
Drank wine and fell to floor	0	1	1
Fell and hit head, confused	0	2	2
Total	28	72	100

It is important to know why patients are admitted to the mental hospital. Why did the family, the friend, the general hospital, or the nursing or old age home give up the patient? Too often the family is accused of "dumping" the patient in the state mental institution. Yet, the duration of symptoms prior to admission, so frequently well over 2 years, points to the fact that the family kept the patient home until the situation became desperate. In Table 10 we see that in 60% of the cases, the patient became unmanageable at home. This is described in the records as disturbed behavior, yelling at night and waking neighbors who complain, confusion, wandering away and getting lost, etc. Note that in 14% the patient became unmanageable in another type of institution, namely, general hospital, nursing home, or home for the aged.

TABLE 11

Reasons for Admission—Psychosis With CAS

	M	F	T
Tuned on gas and forgot to light it	1	1	2
Unable to care for patient at home (confused, unmanageable, disturbed, etc.)	31	44	75
Unmanageable in other institutions (nursing home, general hospital, home for the aged)	7	6	13
Suicidal attempt	0	3	3
Unable to care for self	0	3	3
Advice of physician	1	0	1
"Blacked out" on street	1	0	1
Fell and hit head, got confused	0	2	2
Total	41	59	100

Table 11 shows a similar situation in the arteriosclerotic psychotic with an even higher percentage (75) of those unmanageable at home.

Conclusions

From our present study the following facts emerge:

1. Patients suffering from psychoses of the senium in 1957 came to the Brooklyn State Hospital after a longer stay at home than they did in 1943. This may be due to a better public understanding of our older aged citizen and hence greater tolerance; better health services in the community; the widespread use of antibiotics and tranquilizers; the establishment of more facilities like "golden age clubs" and day care centers for the aged; and social security benefits which help support the older person and maintain his dignity.

2. Patients admitted in 1957 are older than those admitted in 1943. More of them, however, remained alive.

3. Among those who died, there was only a slight difference in the percentages in both studies of those who died within one month. In the 6 months' period after admission, however, a greater percentage died in the 1957 series, than in the 1943 group.

4. The reasons for admission in both studies were similar, the most prominent reason being inability to care further for the patient at home or in the community.

5. The number who left the hospital was the same in both studies, but the number who remained in the hospital was greater in the 1957. These will now be studied to determine how many, if any, could be returned home, where, with a little guidance, the family or other facility might manage them. It may be that such a study will suggest a particular type of facility.

It is our hope that some day there will be available at the level of the local community, the means by which many of the aged afflicted with a mental condition, may be cared for at home without the necessity of admission to a state mental institution. Also, it may be possible through similar means to keep at home those who have improved at the mental hospital and have been discharged.

Gonadal Immaturity as an Etiological Factor in Some Forms of Mental Deficiency, and Its Therapy

HAROLD H. BERMAN, M.D., KATHRYN ELEANOR ALBERT-GASOREK, PH.D., and MAX REISS, M.D., D.Sc.

This report has to do with the results achieved in a circumscribed group of boys who were destined to be life-long mental defectives. They had in common, in addition to their mental deficiency, retarded genital development. Halkerston et al.,[1] described two years ago, an interesting syndrome in which the testicle, owing to an open inguinal canal, fluctuates between the scrotum and the abdomen. We studied a group of psychotic and neurotic patients who showed this syndrome and, particularly, a group of mentally defective boys between nine and fifteen years of age. These last are the subjects of this report. We have begun a much more elaborate investigation on a larger group of boys and we hope to report on them in the future.

We are dealing here not with cryptorchid testicles fixed in the inguinal canal but testicles which freely retract within the abdomen and sometimes for a long period. In some boys here, the testicle is high up in the scrotum; it retracts with every step he takes. In others, the retraction takes place when they bend backwards or lie down. This syndrome does not disappear of its own accord. We have seen it in young men 24 years of age of all intellectual levels. Again, we have seen it in some men as old as 50 and some much older. Some of these patients tell us that they "lose" their testicles for days at a time.

The pathological significance of this syndrome from an endocrinological as well as a psychiatric point of view is evident. The testicles live outside of the body. Nature provided this for a definite and specific reason. The temperature of its environment must be lower; this is opposed to the ovary which must reside in a warmer climate within the abdomen. The higher temperature, when the testicle resides within the abdomen or within the inguinal canal, produces degenerative changes. Bullmore, Reiss and Smith[2] described the psycho-pathological significance of this syndrome and its resultant immaturity which they claim leads to various neurotic and psychotic states, at times necessitating admission to mental hospitals. They point out a particular type of personality in which the individual is shy, retiring, makes no attempt to defend himself, where there is a complete absence of aggressiveness. Bradley[3] in discussing immaturity, points out that these patients lack overt aggression, they are timid, have complaints of feelings of inferiority with a difficulty in making friends, with little interest in competitive sports or success in jobs and found a tendency toward dependency on the mother or mother figure and poor or perverted sex drive. They describe results of their treatment with chorionic gonadotrophic hormone and claim interesting therapeutic results.

In February of this year at Willowbrook State School, we screened mental defective boys between the ages of nine and sixteen, and found that very few showed normal gonadal development; secondary sex characteristics were deficient as well. There was no pubic hair and no axillary hair. We found them puny in size, with facial characteristics completely undeveloped and the entire body retaining the infantile outline. They were pale, under-sized and under-weight in spite of having received a well-balanced hospital diet. They were shy, withdrawn, were afraid of the examination but did not protest. They were timid on the ward and lacked aggression.

We selected 32 boys from this group and started them on chorionic gonadotrophin in varying dosages from 100 units a day to 1500 and, in some cases, 2000 units per day. In most cases, we were able to cause the inguinal canal to close and to increase the size of the testicle to make its retraction impossible. During the first two months, the boys

From Willowbrook State School, Staten Island, N. Y.

grew in height by an average of 1½ inches. After three months, they had gained at least 2 inches. Even after the drug was discontinued, many continued to grow. This phenomenon was observed without exception. Figure 1 shows the growth in one of these boys treated with the hormone. The dotted line shows his increase in height. After 23 weeks, he had grown a little more than 2 inches (Figure 1). His weight had increased from 63 lbs. to 73 lbs.

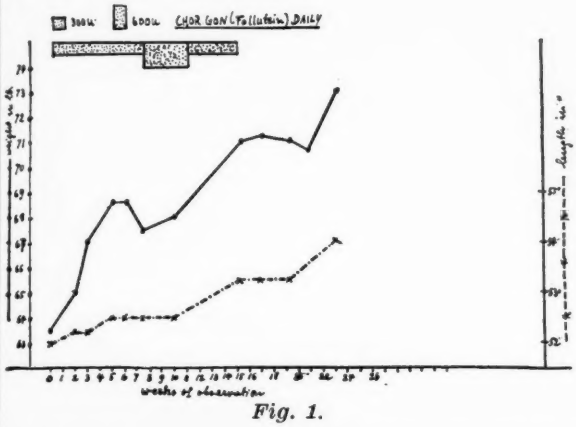


Fig. 1.

We wish to point out that in some of the boys we found an unsuccessful orchidopexy performed for cryptorchidism. In these we saw Frohlich's syndrome beginning. In some there was complete absence of one testicle. Treated with chorionic gonadotrophin they also gained in height and weight and showed remarkable improvement psychologically but did not retain this improvement when the injections were stopped. We attribute this to the fact that there was too much scar tissue to permit the testicle to descend once the operation had been performed. Therefore, we strongly urge that, before any operation such as orchidopexy is planned, a trial of intensive treatment with chorionic gonadotrophin be attempted. Figures 2 and 3.

In addition to this, the most intriguing change we found to be the facial expression. This is seen in the examples shown in Figures 2 and 3 where the facial changes during and after completion of treatment are recorded. The facial stigmata of the dullard have nearly disappeared. Another notable feature is that the behavior changes. These patients have been captive of the factors which produce limited intelligence, limited contact with the environment, looking

Fig. 2.

Fig. 3.

from below up with feelings of inferiority, frustration and inaptitude. We released them from these states. Boys who were shy and rarely spoke, spontaneously became social, sometimes aggressive, before they settled down into a mature state. This is a maturation process. As we examined them, we found that they were beginning to think. Before this, they were inaccessible to teach-

ing. Now, we have made them, to resurrect a term, "free to gain." In other words, they are now in a state where they can be reached by a teacher.

In treating these conditions, we must not be caught unprepared the way we were with the psychotics when we freed them from the introspection and introversion of schizophrenia with the tranquilizing drugs without having a program for them. We must have a program in which to stimulate their interest along proper channels. It must be remembered that a great deal depends upon the guidance given these boys at the critical moments. Along with our study, we are also trying to determine the extent to which improvement from the somatic immaturity can influence the mental state. Here we think is the basis for future research with the correlation of psychiatry and clinical psychology.

The psychological tests were all carried out according to the principle of objective blind testing. The range of intelligence (revised Stanford-Binet) in the treated and control groups was from idiot to borderline and in terms of pre-treatment I.Q. we have been able to show that the groups are not statistically incomparable. Pretreatment I.Q. for the untreated group averaged 46.7 with a standard deviation of 9.86, while pretreatment I.Q. for the treated group averaged 47.5 with a standard deviation of 10.5. The average change in I.Q. following approximately three months' treatment for the treated group was 7.0 points with a SD of 5.1, while average change for the untreated group was 1.9 with a standard deviation of 3.6. This difference does not appear attributable to chance and is ($p<.01$) probably representative of a real difference.

In going through the Bender Gestalt drawings we were impressed with the changes which we saw in many of the treated patients. Figure 4 gives an example of the type of change seen in some of these boys' reproductions. While individuals in the control group also showed changes it was our impression that the changes were less marked than in the treated group. To check this we rated drawings following the standards published by Bender,[4] and also according to the system developed by Pascall and Suttell.[5] It is difficult to extract from the mass of data thereby elicited any general group trends which could be reported with confidence at the present. Where, for example, does one place a rating for a design which is superior to that given as typical by Bender for 6 years (Design 7) but not as good as that placed by Bender at year 10; and what degree of validity has any change in the rating so assigned. We have, therefore, decided not to present, at this time, statistics but to confine ourselves to consideration of the trends seen by inspection. Figure 4.

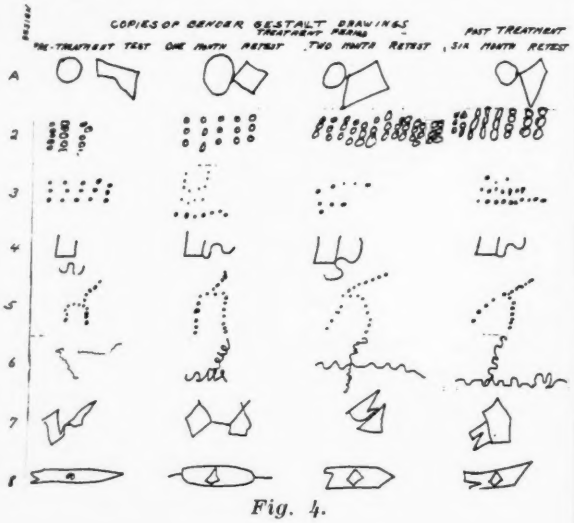
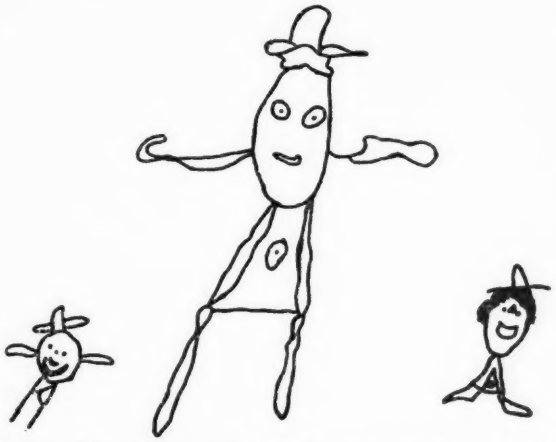


Fig. 4.

In many cases, the size of the drawings definitely increased and while group averages also indicate that treated boys used more paper than untreated boys in reproduction of designs while on treatment, there is some overlap between groups and we only wish to report it and not to speculate on its significance at this time. Analysis of the Human Figure and other non-copied drawings while not complete, reveals the same trend toward increase in size of the drawing which was found to be fairly typical for the treated group's Bender Gestalt reproductions. Figure 5 illustrates the change in male figure drawings of one patient. Here, as for the treated group, generally (although not without exception) the change is readily apparent and appears to be related to the treatment. We are not prepared, on the basis of our present knowledge, to offer a final interpretation of this change although we believe

it to be related to the patient's feelings of self-esteem and willingness to have attention focused on them, i.e. the opposite of wanting to escape attention because of feelings of inferiority.



Pre-treatment During treatment Post-treatment

Fig. 5. Tracings of male figures drawn.

The teachers evaluated the patients' progress independently. In the beginning, there was a discrepancy in the points of view between the psychiatrists and the teachers. Whereas self-assertion and aggression in the boys was considered by the psychiatrists as a welcome feature, the teachers considered it a fact disturbing the class discipline. The boys, released from the restricted world in which their mental deficiency held them captive, now become aware of their increased capacities and have a desire to progress. This points out that a new method of classroom teaching will be required in these cases. The changes in handwriting are of interest. The improved legibility of the handwriting is concomitant with the improvement clinically. Some of the boys who did not write previously are now writing. Figures 6 and 7 illustrate the changes in the writing of two boys during and post-treatment.

We should like to state that it is not our intention to treat these patients with the purpose of making a lower grade mental defective into a higher grade mental defective but rather, we are aiming to produce a therapy which will allow these patients to return to live in the community in a so-called normal environment, in spite of an I.Q. which has not reached the level of a normal child.

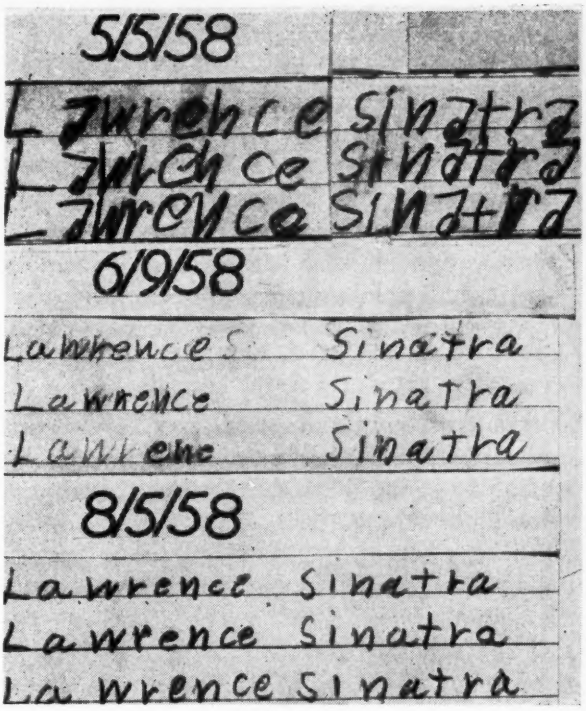


Fig. 6.

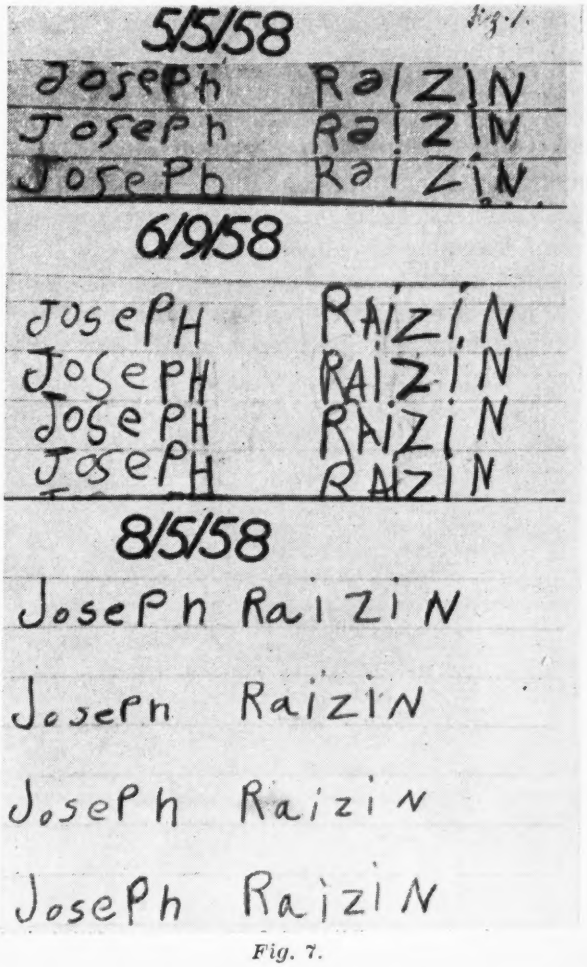


Fig. 7.

Summary and Conclusion

We are reporting the observations in a pilot study in which we have demonstrated in 32 hospitalzed boys wth somatic immaturity and mental retardation that intensive treatment with chorionic gonadotrophic hormone not only brings about marked physical development with linear and muscular growth, but also marked alteration of the mental status with improved accessibility, cooperativeness, and teachability so that the patients become amenable to psychotherapy, school instruction and vocational training.

Again, we should like to add our word of caution to those we know will be spoken by individuals who have to deal with parents and others keenly interested in the progress and welfare of one particular child. Chorionic gonadotrophin is not, by itself as we now see it, the cure for mental deficiency, or even for one form of it, but it appears to provide an important basis for instituting successful psychiatric therapy. The present findings are merely to be considered as leads for further research. In any case, these results open new avenues. Results thus far obtained bear out our theory that in a certain group of mentally defective boys where sexual retardation is one of the predominant features, its repair produces a state in which they are able to make better use of their limited capacities.

From this paper, we hope we have shown that in a limited group of mentally defective boys where sexual retardation is one of the predominant concomitant features, its repair produces a change of personality and emotions. We have made our patients "free to gain." The rest is up to us. We hope this treatment can be carried on as a preventive measure; that in early infancy when the testicles are found to be too easily retractable or living high up in the scrotum, proper measures will be instituted to prevent conditions which result in so-called mental deficiency and Frohlich's Syndrome and various other defects in personality.

This is a preliminary report from which final conclusion cannot be drawn.

Authors' Note: We want to express our thanks and appreciation to Squibb Pharmaceutical and Research Department for making available to us supplies of chrionic gonadotrophin (Follutein) used in this investigation.

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The Aging Process — Physiologic and Pathologic

GEDEON EROS, M.D.

This presentation included the demonstration of the discussed macroscopic and microscopic structural and histochemical changes.

I should like to discuss the problem of aging from the point of view of the pathologist. I shall try to summarize the morphologic changes of the central nervous system in normal and pathologic old age. We pathologists are often asked by the clinicians whether these changes are the morphologic manifestations of inevitable involutional regressing processes, or changes caused by diseases of old age. If they are caused by diseases, what is the etiology and cure of these diseases, and what measures could prevent their development. These problems came in the foreground especially in the last few decades, because of the ever increasing age shift of the population toward the older age groups, and the considerable increase of the number of elderly mental patients in mental institutions.

There are certain changes in almost all the organs and tissues of the body, which are the result of a progressive inevitable physiologic involution. We find these changes not only in the skin, musculature, bones, endocrine glands, circulatory organs, respiratory organs, and urinary system, but also in the central nervous system. The involutional changes are characterized by the gradual loss and atrophy of the parenchyma, and the increase of the functionally less valuable interstitial tissue.

In the central nervous system the involution usually starts at or about the age of 40 but there is no general rule in this respect. The degree of the morphologic changes greatly varies in different individuals. I often saw more severe changes in the brain at the age of 45 than at the age of 70.

Changes of the brain can be noticed by the naked eye only in those cases where the involutional changes are far advanced. In these cases the brain is smaller, and its weight less because of the diffuse atrophy. The meninges are usually thicker than normal, the ventricles are dilated, the gyri are smaller, the sulci are wider and deeper, and there is an increased amount of cerebrospinal fluid in the dilated subarachnoid space and the dilated ventricles. The cortex shows a deeper color. Proportional atrophy can be seen also in the white matter, large subcortical ganglia, thalamus, brainstem, and cerebellum.

From Brooklyn State Hospital, Brooklyn, N. Y.

Microscopically, the soft meninges show thickening, especially over the convexity of the brain near the midline along the Pacchionian granulations. In the cerebral cortex there is rarefaction of the nerve cells with circumscribed and diffuse areas of disappearance of the nerve cells. In less severe cases the normal cytoarchitecture of the cortex, however, is only slightly disturbed or not at all. The nerve cells show different degenerative changes. The Nissl substance, especially in the larger nerve cells, is diminished in amount. One of the most common and earliest degenerative changes is the deposition of a yellowish lipochromic pigment in the cytoplasm of the nerve cells, replacing the Nissl bodies around the nucleus. This is the so-called "Abnutzung pigment" or "wear and tear pigment" which can never be seen in the nerve cells of normal children. In addition to this pigment, lipoid substances are deposited in the nerve cells. These are especially abundant in senile psychosis.

Another change of the nerve cells is swelling with disappearance of the Nissl substance, and displacement of the nucleus. More common is, however, pyknosis, shrinkage of the nerve cells. These nerve cells are narrower, darker staining, and their axons are wavy, corkscrew-like.

All three types of the glia cells are increased in number in the cortex, the microglia, oligodendroglia cells and the astrocytes. The micro- and oligodendroglia cells show the increased phenomenon of satellitosis, and also certain degree of neuronophagia may be present. The glia cells also show degenerative changes. The microglia cells may be elongated, taking the appearance of the so-called rod cells, or are transformed

into scavenger cells. There are usually scavenger microglia cells loaded with fat in the perivascular spaces. The oligodendroglia cells may show peculiar mucoid degeneration. There is also an increase in the number of astrocytes in the cortex, and increased amount of fibrous glia, representing the proliferation of the interstitial tissue, especially in the upper layers of the cortex near the pia, producing thickening of the piaglial membrane. Degenerative changes can be present also in the astrocytes, swelling and disintegration of their processes. Sometimes, the glia cells are much larger than normal.

Similar changes are present also in the basal ganglia, thalamus and brain stem, in lesser degree in the medulla, cerebellum and spinal cord.

The white matter shows an increased number of astrocytes, and an increased amount of fibrous glia with a peculiar degeneration of the oligodendroglia cells. The degenerated oligodendroglia cells show round inclusion bodies stained by basic dyes, the so-called amyloid bodies. Amyloid bodies can be very numerous in the aging brain. The myelin sheaths and axons of the white matter show only minor changes.

There are certain changes also in the arteries of the central nervous system. The wall of some small arteries of the brain, especially in the lentiform nucleus, shows iron calcareous deposits, which are not regarded as an arteriosclerotic change. The small arteries may also show atrophy of the media, and hypertrophy of the adventitia as pure regressive changes, independent of arteriosclerosis. We often see the looping of the arteries, caused by the general atrophy, and less tension. A peculiar vascular phenomenon of the brain in old age is the new formation of the capillary and precapillary blood vessels in the gray matter. The newly formed small arteries are arranged in packets, bunches, probably representing compensatory proliferation.

These are the commonly found changes in the central nervous system in old age. As I mentioned before, these changes vary greatly in intensity in different persons of the same age. Furthermore, none of these changes can be regarded as specific of old age. Similar changes can also be caused by different toxic, infectious, and endogenous damage accumulated throughout life. These changes cannot be entirely separated from vascular damage either, and arteriosclerosis is frequently present in the brain of older individuals.

In spite of the fact that arteriosclerosis is considered a disease of the arteries, and not an aging process, on the basis of my studies I firmly believe that certain changes of the cerebral arteries, considered as arteriosclerotic changes, belong to the involutional aging processes. As a rule, these involutional vascular changes start quite early, and I think they represent the initial stages of arteriosclerosis, indicating that the aging process of the arteries cannot be completely separated from arteriosclerosis.

As I have observed[1] early arteriosclerotic changes are expressed by the splitting of the elastic membrane which gradually progresses into the characteristic changes of arteriosclerosis and atheromatosis. I was able to differentiate between two types of arteriosclerosis of the cerebral arteries: the hyperplastic and the hypoplastic. I believe that the two types are determined by constitutional factors. In certain individuals the degenerative changes of the elastic membrane and the intima, characteristic of arteriosclerosis, are preceded by marked splitting and proliferation of the elastic membrane, in others we cannot observe any hyperplastic elastic changes, only primary degeneration of the elastic membrane. I have seen the hypoplastic type combined quite often with severe senile changes of the brain.

In old people senile and arteriosclerotic changes are often combined and arteriosclerosis also may produce degenerative nerve cell changes, rarefaction of the nerve cells, and proliferation of the glia cells with satellitosis and neuronophagia, very similar to those caused by primary involution. Furthermore, how can we be sure that some of the above outlined nonspecific changes were not caused by various toxic and infectious factors during life?

Since all these changes are not specific, and the same changes can be produced by different factors, on the basis of morphology alone we cannot make definite etiologic considerations. We can only say that these are

the changes seen in old individuals. They greatly vary in intensity in different persons of the same age and the difference is only gradual between the changes of normal and pathologic old age. In pathologic old age the above outlined morphologic changes are usually severe with the addition of other changes. These other changes are the senile plaques and the Alzheimer's neurofibrillary changes.

The senile plaques develop in the cerebral cortex, corpus striatum, thalamus, and in lesser degree in the cerebellum, but never in the medulla, spinal cord, or white matter. Usually they appear earliest in the Ammon's horn. They are never seen in other organs. The senile plaques are rounded masses of argentophilic debris invaded by microglia cells and surrounded by astrocytes. We do not know anything about the mechanism of their development and etiology. They may originate from the intercellular or cellular substance as the manifestation of a metabolic disturbance, or an exogenous toxic damage of the aging brain of human beings. Senile plaques are never seen in the brain of animals. Experiments to produce them in animals, even in higher mammals and apes, are without any success. Furthermore, they are not absolutely pathognomonic of senile psychosis. Senile plaques can be seen also in normal senility, in a variety of other neurological conditions, and they may be absolutely absent in severe cases of senile psychosis. They are rather characteristic of senile psychosis, however, if they are present in large number. I can say that since senile plaques in the great majority of cases are seen in the brain of old or aging individuals, their development is related to the altered metabolism of old age.

Another rather characteristic morphologic change in senile psychosis is the Alzheimer's neurofibrillary change. In a normal nerve cell there are numerous fine regularly arranged neurofibrils. The Alzheimer's neurofibrillary changes will show fusion of these fibrils into one thick bundle which is arranged in the shape of a loop, circle or spiral. This change again cannot be regarded as specific of senile psychosis, or the result of physiologic aging. It also can be seen in other conditions.

As stated before, senile psychosis is usually combined with pronounced arteriosclerosis. Very few pure forms can be seen. Accordingly the patchy or diffuse nerve cell destruction in abnormal old age can be the result of vascular damage or senile involution. The study of the vascular pattern of the cortex in senile psychosis many times shows patchy or diffuse disappearance of the vascular bed in the same areas where the patchy or diffuse rarefaction of the nerve cells is present. This picture is often combined with senile plaques, abundant fat in the nerve cells, and marked gliosis.

In summary, all the aforementioned changes of the central nervous system in physiologic and pathologic old age are the combination of physiologic involution, damages caused by toxic, infectious and metabolic factors during life, and vascular changes and diseases of unknown etiology superimposed on the aging tissues. I do not regard the senile plaques and the neurofibrillary changes as involutional processes. I believe they are pathologic changes of still unknown etiology, somehow related to the altered metabolism of old age. I want to emphasize that if they really are the manifestations of a disease, their development could be prevented. Similarly, the arteriosclerosis, which is not purely an involutional process, but a disease superimposed on aging arteries, may not only be preventable, but also curable. It seems obvious that genetic factors are important in the development of these changes, as it is also indicated by Kallmann's studies of aging twins.[2]

Now let us consider the so-called presenile psychoses. The pathogenesis and etiology of these conditions are as obscure as in the senile psychoses. The presenile psychoses show some common characteristics. They occur in the presenium, usually between the ages of 45 and 60. Clinically they are characterized by progressive mental deterioration combined with focal neurologic symptoms and pathologically by progressive diffuse degenerative changes of the nerve cells with gliosis especially in the cerebral cortex, occasionally combined with degenerative changes in other parts of the central nervous system.

Alzheimer's disease is clinically character-

ized by rapid progressive mental deterioration and multiple focal neurologic symptoms. The pathology in this disease is almost the same as in senile psychosis, only much more severe. There are marked diffuse degenerative changes of the nerve cells in the cerebral cortex, basal ganglia, thalamus, and in lesser degree in the cerebellum with innumerable senile plaques, and neurofibrillary changes. There is abundant fat in the nerve cells.

The occasional familial incidence indicates probable constitutional factors and the senile plaques and neurofibrillary changes probably represent an organic damage caused by metabolic or toxic factors occurring in the presenium. This disease was found in a few cases in individuals as young as age 20.

In Pick's disease the clinical picture is somewhat different and the microscopic pathology is entirely different from that of Alzheimer's disease. It is clinically also characterized by progressive mental deterioration and focal cortical symptoms. Pathologically, there is circumscribed atrophy of the cortex and white matter, not diffuse atrophy as in Alzheimer's disease. The destruction of the nerve cells in the atrophic areas of the cortex is severe. There is also myelin sheath destruction in the white matter of the atrophic areas. There are no senile plaques and neurofibrillary changes, but in the nerve cells sometimes peculiar round argentophilic bodies can be seen. Mostly the frontal, parietal, and temporal lobes are affected, but there are cases in which only part of a lobe shows atrophy.

The pathologic changes in Pick's disease cannot be regarded as precocious involutional changes. They have to be regarded as changes caused by a disease occurring in the presenium, the etiology of which is completely unknown. There are definite indications that in Pick's disease gene-specific changes play an important role, and endogenous or exogenous unknown pathologic factors damage the brain hereditarily predisposed to this damage. Pick's disease quite often develops also in the late senium. It is not a strictly presenile condition.

Another condition which belongs to the presenile dementias is the Jacob Creutzfeldt's disease. Clinically, it is characterized by progressive mental deterioration and spastic paralysis. The pathology includes diffuse degenerative changes of the nerve cells in the cerebral cortex, basal ganglia, and spinal cord, and non-systematic severe destruction of the myelin with foci of complete necrosis. Again senile plaques and neurofibrillary changes cannot be seen in this condition. This disease of unknown etiology is somewhat similar in its clinical manifestations and pathology to pellagra which is a deficiency disease.[3]

Another supposedly presenile dementia is Kraepelin's disease which is clinically characterized by rapid mental deterioration with anxiety, depression, and psychomotor restlessness. Often speech defects are present with peculiar catatonic-like motor symptoms. The pathology in this variety includes severe diffuse degenerative changes of the nerve cells in the cortex without senile plaques and neurofibrillary changes. The etiology is again unknown. It is only suspected that toxic factors may play an important role.

Another condition which is recognized by some investigators as a presenile dementia, is dementia with cerebellar atrophy. This variety, which also occurs in the presenium, is characterized by severe progressive mental deterioration with cerebellar symptoms. The pathology includes degenerative changes of the nerve cells in the cortex and degenerative changes of the cerebellum without senile plaques and neurofibrillary changes. The etiology is unknown and the disease seems to show some familial tendency.

In all these presenile psychoses clinically there is a progressive mental deterioration combined with some focal neurologic symptoms according to the localization of the degenerative changes. I believe, that these are disease-entities of different etiology superimposed on the aging brain, and in their etiology genetic factors play an influencing role.

The important question regarding senile dementia, and presenile psychoses is, what etiologic factors are producing the pathologic changes in these conditions? In this connection I want to emphasize that it is impossible to determine the etiologic factors from the above outlined morphologic changes. None of them are absolutely specific of old age. It is true, however, that

very few diseases produce specific organic changes in the central nervous system. Myoclonus epilepsy, tuberous sclerosis, and Tay-Sachs disease are almost the only diseases of the central nervous system which produce specific changes not seen in any other conditions. The morphologic imprints of almost all the other diseases, except inflammatory conditions and tumors, are nonspecific. In addition, the nervous system can respond to entirely different stimuli the same way. To this I could add that changes of the biological behavior of the cells are not always accompanied by morphologic changes. This is especially true for the organs of the endocrine system and the central nervous system. I can only state that the changes of the central nervous system in pathologic old age are the combination of physiologic involutional and pathologic processes.

Another question recently emphasized by investigators, is to what extent are the organic pathologic changes responsible for the mental symptoms. In some cases there is marked discrepancy between the severity of the pathologic changes of the brain and the mental symptoms. Severe pathologic changes can sometimes be seen in normal senility and rather slight changes in psychosis. This discrepancy seems to indicate a role for the personality in addition to the organic damage. The central nervous system has a tremendous reserve power which can compensate for damage. In certain types of personality, however, environmental and social stress may upset the balance between the organic damage and the compensatory power of the brain because of the unusual vulnerability of this type of personality to environmental and social stresses. (Rothschild, Malamud.[4,5])

As I have indicated, this is a complex problem, and the pathologist alone on the basis of morphologic studies with the available conservative methods at present is unable to solve it. We have to swing back again from the old Virchowian principle of the purely morphologic cellular pathology to the humoral pathology, looking for the imprints of diseases not only in the morphologically visible structural alterations of the cells, organs, and tissues, but also in the changed chemistry of the cells and body fluids.

Few investigations have been made in connection with the biochemistry of the developing, mature, and senile brain.[6] We know that the brain in old age shows a marked decrease in total solids. The extracellular water, sodium, chloride, and calcium show a definite increase in the aged central nervous system, whereas potassium, magnesium, phosphorus, nitrogen, lipid compounds, ash, and intracellular water show decrease (Himwich[7]). We need more thorough chemical studies which should include biochemical investigations of the blood, other body fluids, and the tissues and organs themselves. Morel especially emphasized the study of the serum proteins in senile and presenile conditions, recommending ultracentrifugation, electrophoresis, and chromatography.[8]

The innumerable enzymes in the body seem to play an important part in the metabolic processes, and the measurement of the activity of certain enzymes may indicate certain pathologic conditions. The activity of certain enzymes measured in the blood and in other body fluids have given valuable information about certain pathologic tissue change. The markedly increased amount of acid phosphatase in the blood in the presence of carcinoma of the prostate gland with mestastases is the only reliable cancer test today (Gutman[9]). Different types of tissue damage can be detected during life by the determination of the transanimase activity in the blood (La Due and Wroblewski[10]). The serum aldolase activity seems to be an aid in the differential diagnosis of neuromuscular disorders (Aronson and Volk[11]). One is justified in calling these procedures biochemical biopsies which at the present time are still few and may indicate not only organic structural damage, but also hidden adverse changes in the normal biological behavior of the cells. However, this does not always produce morphologically visible alteration in the cell structure. These studies can be aided by comparative animal studies and animal experiments.

I regard the direct application of histochemical methods on tissues and cells as a most promising approach. These methods make possible the study of the chemical metabolic changes and enzymes in different

cell and tissue systems. Gomori was one of the pioneers in this field. One of his best known histochemical methods is the demonstration of acid phosphatase in histological sections of the prostate gland and cancer of the prostate gland.[12]

Roizin[13] studied the behavior of enzymes in the aging brain in histochemical reactions and he was able to demonstrate the decrease of oxydase enzymes in the nerve cells of the senile brain. He found that the oxydase enzymes are bound to the protein compounds of the Nissl bodies. The decreased amount of enzyme in the cell explains the slower metabolism and respiration of the aging nerve cell resulting in the accumulation of lipid substances in its cytoplasm. On the basis of his histochemical reactions Roizin was able to differentiate between different types of oxydase enzymes in the nerve cells. He also applied Gomori's acid phosphatase technic on brain tissues and found differences between the acid phosphatase content of normal and aging nerve cells. Morel studied by histochemical reactions the metabolism of nucleoproteids in nerve cells affected by neurofibrillary changes.[8]

It seems to be plausible that instead of mass chemical studies of the entire brain, it is more helpful to study the chemistry and metabolism of different tissue and cell systems separately, in order to understand better, the interrelationship between some specific histometabolic disorders and certain pathologic conditions. This new approach could be called cellular pathochemistry. It is still in its infancy but offers tremendous possibilities for the future, especially if fresh biopsy material will be studied.

In closing, I want to say that the pathologist must admit that he cannot solve the secrets of old age from the study of the structural changes alone, in spite of the sometimes severe organic changes. He cannot determine, from reading the structural changes, the factors leading to normal or pathologic old age. I feel that new methods of investigation are needed to broaden the old concept of structural cellular pathology, and that biochemical and histochemical studies can contribute more to the understanding of the changed biologic behavior of aging cells than morphologic studies. The situation in the aging problem is almost the same as in the cancer problem.

Even if the new methods of investigation will explain the pathogenesis of the organic structural changes of the central nervous system in normal and abnormal senility, still other problems of aging have to be solved. Other problems of aging, such as the role of heredity in the development of the structural chemical changes, and the role of the personality and social factors in the development of the mental symptoms are equally important factors necessitating further research.

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Unidirectional Current, Modified by Succinylcholine in Electroconvulsive Treatment of the Aged

JAMES E. RAPPA, M.D., and HERMAN TANOWITZ, M.D.

When Cerletti and Bini introduced electroshock therapy (EST) in 1938 they gave psychiatry a most effective tool, not, however, completely free of risk. Despite the availability of drugs and equipment to minimize the danger of EST today, 20 years after Cerletti and Bini, fractures and dislocations are still encountered. In 1954 Wolff et al.[1] reporting their results with EST on 249 women, between the ages of 70 and 80, state, "there were *only* 8 fractures." This shows that in more than three out of every hundred patients a fracture occurred. In 1955, Ehrenberg et al.[2] using conventional EST, without benefit of "curare-like drugs," showed that 112 patients had the following complications: four compression fractures of the spine, one EST death, three deaths due possibly to shock. Here with non-modified EST there was a certain 5% and a possible 8% complication rate. In their conclusion, the authors comment on the fractures by stating

"The occurrence of only four fractures in 1329 EST's appears to indicate that diminished muscle bulk compensates for the seemingly increased risk of osteoporosis, and makes the use of curare-like drugs unnecessary."

We do not agree with this conclusion.

In 1954 DeWald and Margolis[3] conclude from their series of 263 patients, treated, with and without muscle relaxants, that fractures are more likely to occur in men than in women, that age has no statistical value in predicting the occurrence of a fracture.

"From our series it would seem that the only physical factor that definitely predisposes to fracture is the presence of osteoporosis."

"It has been our practice to use a muscle relaxant prophylactically in those patients whose preshock examination shows findings that would predispose to fracture such as osteoporosis or large muscle mass."

In 1957 Impastato et al.[4] found that in 100 succinylcholine treated patients there were no fractures while in 100, given unmodified ECT, there were seven vertebral fractures. Furthermore, the authors go on to state:

"In the presence of osteoporosis . . . higher doses sufficient to abolish all muscular movement are advised."

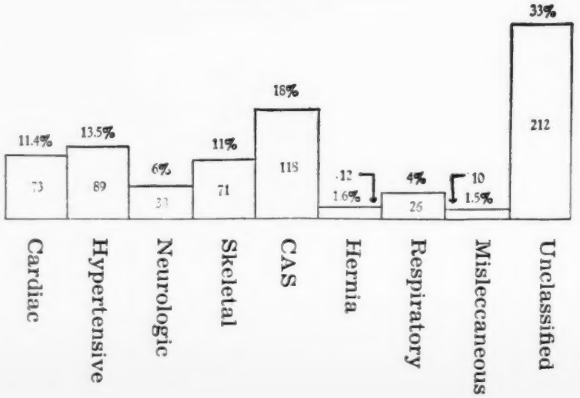
This difference of opinion regarding modified vs. unmodified shock is our reason for presenting this paper. This is the second of three papers we have planned, the primary purpose being to attempt to convince even the most skeptic of the high degree of safety of modified EST even in the poor risk patient.

Our first paper[5] published in October 1957 gave a preliminary report on the use of unidirectional current modified by succinylcholine and was limited to a discussion of techniques used. The third paper, to be published in the near future, will give the psychiatric results of treatment.

The statistical analyses about to be presented were derived from a project begun in the early part of 1949 at which time one ward of Brooklyn State Hospital was set aside for the purpose of administering EST to male patients, referred from all parts of the hospital, whose physical condition rendered them potential risks if given the unmodified form of treatment. A total of 649

CHART No. 1

TOTAL: 649 PATIENTS



From Brooklyn State Hspital, Brooklyn, N. Y.

CHART 2

PRE-TREATMENT

Drug	*Dosage Range*
Atropine	0.6 - 2.4 mg
Aminophyllin	250 - 500 mg
Digalen	.5 - 1.0 USP units
Etamon (T7A)	200 - 300 mg
Benadryl	25 - 50 mg
Quinidine	200 - 400 mg

TREATMENT

Drug	*Dosage*
Pentothal Sodium / Surital / Nereval	250 mg to 400 mg
Succinylcholine Cl.	20 - 80 mg
O_2	
Reiter Shock	

POST-TREATMENT

O_2
Aspiration
Norepinephrine

patients ranging in age from 50 to 85 years received treatment. Out of this number contraindications were shown in 437 patients. Chart No. 1 lists the number and variety of contraindications encountered in our patients. Many of the contraindications listed here include several sub-types. For example, under cardiac involvement there were cases of old coronary occlusion and myocardial infarction, the most recent occurring approximately one year prior to treatment; various arrythmias and rheumatic heart disease. Under neurologic, representative types included hemiparesis, hemiplegia, Parkinsons, multiple sclerosis, post-operative brain tumor, peripheral nerve injuries, old polio, aphasia and one case of thalamic syndrome. In the skeletal group there were some recent and ununited fractures including fracture of the zygoma, compression fractures of the spine, osteoporosis and osteoarthritic lipping. Under miscellaneous there were two cases of recurrent dislocation of the jaw, one recent dislocation of the shoulder, three diabetics and four cases of rheumatoid arthritics. All 437 had an EKG analysis prior to treatment. Diagnosis of osteoporosis or osteoarthritic lipping, was made by x-ray. Such conditions as hypertension, cerebrovascular accident or generalized arteriosclerosis were in most part clinically determined.

All types of symptomatology and diagnostic categories were treated. In consonance with most other workers we found that where the pure affective component was dominant fewer treatments were needed and a more favorable prognosis could be expected. The presence of delusions, somatic fixations and gross sensorial defects, in that order, made the prognosis less favorable.

In the course of 10 years our technique varied in accordance with newer drugs and methods as introduced and recommended by other workers. Basically we followed the same pattern used by Impastato, Richardson, Lewis, Gahagan, etc.[6] and others. After using Intocostrin and decamethonium bromide for a short time along with alternating current—the Rahm and Medcraft machine, we finally settled on a standard routine of barbiturate anesthetic, a muscle relaxant (succinylcholine chloride), and the Reiter machine. The latter was used in various modalities as reported in a previous paper, but in this series all received convulsive therapy. Chart No. 2 lists the three phases of treatment, the drugs and media employed in each phase. Obviously no one patient received all medication, but all except Norepinephrine were used at some time. The latter was available for use.

The types of cases we treated are best represented by the following:

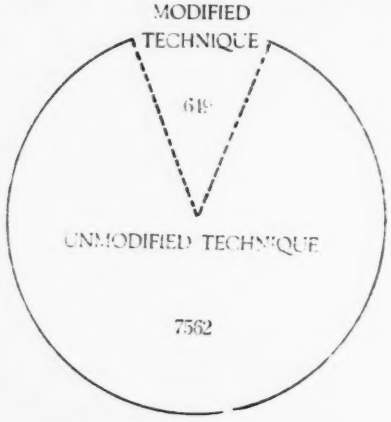
Case No. 1. A 74 year old male, diagnosis of CAS, physical condition on admission described as "poor." He had a bilateral inguinal hernia. X-ray showed osteoarthritis of the spine. EKG reported post. wall infarct with premature ventricular contractions. He was given 10 ECT's and three months after admission was placed on C.S., condition improved.

Case No. 2. A 59 year old male, diagnosis CAS, paranoid, agitated, thought dogs were going to kill his family, sexual preoccupations. X-ray: hypertrophic arthritis. Hypertensive configuration of heart. EKG—Myocardial damage. Received 10 EST's with loss of psychotic manifestations. Placed on C.S. 11 months after admission.

There were many such cases whose physical condition included fibro-calcified tbc., demineralization of spine, old ununited fracture of elbow, hypertensive heart disease, abnormal T, sinus bradycardia, cerebrovascular accident, myocardial damage, compression fractures of several bodies of dorsal spine, recent herniorraphy etc. All of these

were actual diagnostic categories. In one case the cardiologist advised therapy only if absolutely imperative and only under careful supervision. This patient was given 13 treatments and the record revealed no major untoward reaction. Discharged as improved.

E.C.T. TREATMENT
10 YEARS TO 1958—8211 PATIENTS



UNMODIFIED INJURIES

Fractures	46
Compressed Fractures	8
Avulsions	6
Dislocations	4
Cardiac Complications	2
Miscellaneous	4
Total	70

Injury Ratio	1:108
Modified Technique	None

Chart No. 3 is a graphic representation of the comparison of our series of cases with the group treated by standard unmodified techniques in the rest of the hospital and the types and ratio of complications sustained in the non-modified treatment group. The graph shows that in the total series of 649 cases there were no major complications, while in the rest of the hospital treated group there was slightly under 1% complications.

Comment

This paper constitutes one of three covering our experiences with the modified technique of administering electroconvulsive treatment to a series of selected risk cases in the 50 and over group. A total of 649 patients were treated all receiving a barbiturate anesthetic, a muscle relaxant and unidirectional current with the Reiter machine. Of the 649 patients, 437 had a specific physical disability constituting a potential source of post-shock complication, particularly for the cardiovascular and skeletal systems. Where indicated specific autonomic drugs and other supportive measures were used in all three phases of treatment. The complications arising in the group were limited to occasional prolonged apnea and mild transitory dysrhythmia. There were no serious complications. During the same 10 year period 7,562 patients were treated with the standard techniques and serious complications occurred in the order of 1:108.

Summary and Conclusion

Although the individual technique and drugs may vary, employment of any means to reduce the burden of shock on all systems and particularly the cardiovascular and skeletal is important. We have found a combination of a muscle relaxant, O_2 autonomic drugs and unidirectional current an effective combination in reducing EST complications with poor risk patients.

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Methohexital Anesthesia in Electrocerebral Therapy

EMERICH FRIEDMAN, M.D.

The need for an ultrashort acting barbiturate in electrocerebral procedures is believed to be twofold: (a) to reduce the secondary or prolonged effect of anesthesia, and (b) to allow for a more rapid and clearer ambulatory state following treatments given on an out-patient basis. In considering the first reason it would be useful to separate the intrinsic effects of the various forms of electrotherapy uncomplicated by the anesthetic agents, or by the cumulative effects after repeated treatments. The second reason is a practical one; if out-patient treatments allowed for more rapid "clearing" the clinic or office work could be done much more quickly, less bed space would be required and patients could be returned home or into routine activities much more quickly.

Methohexital (originally designated as Compound #25398) is a new oxygen barbiturate. Previous investigations by Stoelting et al.,[1] Wyant et al.[2] and Dobkin and Wyant[3] demonstrated that this drug, used in both animal work and in general surgical anesthesia, was of much shorter action, was much more rapidly eliminated from the tissues and was found to be three to five times more potent an anesthetic agent than commonly used thiobarbiturates. In the use of Methohexital in oral surgery the recovery time was found by Redish et al.[4] to be much more rapid than with thiopental and methitural. This work closely simulated ambulatory pre-ECT work since single-dose administration was the procedure, though the drugs were injected slowly.

The chemical, physical and basic pharmacologic characteristics of Methohexital were adequately described by the above workers. Briefly, its chemical configuration is designated as: alpha-dl-1-methyl-5(1-methyl-2-pentynyl)-5-allyl-barbituric acid (sodium salt). There is no sulfur in its composition and the molecule has been found to contain four optically active isomers each of which seemed to possess different pharmacologic effects.[5] This feature will be mentioned later. The substance is stable in aqueous solution, has an approximate pH of 11.0. There was first some question as to mixing atropine and succinylcholine with aqueous solutions of Methohexital but, as noted later, there was satisfactory compatibility if mixing were done immediately prior to its administration.

Procedure

Methohexital was presented in sterile vials containing 500 mg. of the powder. In the first few trials a 1% solution was made by addition of 50 cc. distilled water and 10 cc. doses were drawn, making 100 mg. per dose. To this was added gr. 1/100 Atropine in solution and succinylcholine solution, containing 10-40 mg. It was found that in three out of ten trials with this amount insufficient depth of anesthesia resulted. In order to standardize the routine as much as possible doses were increased to 165 mg. by adding only 30 cc. to the vial and then adding the atropine and succinylcholine solutions as before. This dose of (approximately) 165 mg. plus 1/100 atropine sulphate plus succinylcholine was mixed in the syringe and given at once intravenously as rapidly as possible through a #23-24 needle, taking less than ten seconds in most instances. The solutions were found to be miscible in the syringe giving no precipitate or undue effervescence. (Actually, if several treatments were to be given in succession the total quantity of atropine solution was added right to the vial with the distilled water so that only the different amounts of succinylcholine were added prior to administration.) In every instance the 165 mg. dose produced anesthesia by the time the injection was completed. The electrotherapeutic procedure would then be applied and then, if curarization persisted, positive pressure oxygenation would be given. A trial of non-convulsive electrostimulation treatments was also given using Methohexital as the anesthetic agent. As a model for such treatments Nasopharyngeal-Bioccipital stimulation[6] was chosen. In these treatments it was found that the only way patients could be given the minimum of three minutes of stimulation an injection of

165 mg. of Methohexital was given as above described with the exclusion of succinylcholine. Then, a second 165 mg. was given intermittently, as the stimulation was being applied. The number of cases, types of treatment and related data are given in Table I. Out of the 72 patients shown in the Table all were treated in the office in an ambulatory manner except for 6 patients whose treatments were started in the sanitarium.

TABLE I

Total Number Patients	72
Total Number Treatments	696
Age Range	20-83 years
Number Patients Considered Poor Risks	14
Cardiovascular Diseases	7
Severe Toxic Psychoses	3
Old Post-Operative Peptic Ulcer	1
Senility	3
(Pregnancy	2)
Number ECT Type of Treatments	452
Number Multipolar Electrocoma Treatments	214
Number Nasopharyngeal-Bioccipital Treatments	30

Results and Findings

It was found in all trials that Methohexital produces anesthesia in less than one minute following administration of the 165 mg. dose. A brief period of apnea, lasting less than two minutes was noted in almost all instances (if the electrotherapy was deliberately delayed). The pulse rate increased an average of twenty at the time of anesthesia, unless, due to anxiety or agitation, it was already 110 or more at the time of injection, when no significant changes were noted. Blood pressure readings taken during and after anesthesia showed less than 20 mm. systolic changes regardless of the initial levels. All of the patients had previously been given one or more of other intravenous anesthetics chiefly thiobarbiturates such as hexobarbital, pentobarbital, amobarbital, thiopental, methitural. The immediate pictures from the standpoint of pretreatment anesthesia were not particularly different from that noted with Methohexital except for two items. In most instances the onset of anesthesia was more rapid though the difference was a matter of seconds and not considered significant for the dosages given. The second difference was that no smell-taste experiences, commonly noted with thiobarbiturates, was noted.

The most important difference noted in this use of Methohexital was the rapidity of awakening. In standard ECT procedures, awakening would occur in five to ten minutes after treatment as compared with ten to twenty minutes with all the other intravenous barbiturates, thirty to forty minutes with pentobarbital and hexobarbital. In prolonged electrocoma modalities awakening was evident at the termination of the usual three minute treatment periods, as compared with thirty to ninety minutes of sleep using other intravenous anesthetics. In many instances the patients would react on awakening as though they had not slept and insisted they had not been treated. In other respects the rapid awakening was followed by much more rapid leaving for work or home. The completion of the entire treatment in an established ambulatory routine was about half the time it took with thiobarbiturates, allowing patients to leave twice as quickly. Complications in the administration of Methohexital occurred with frequencies approximately experienced with other barbiturates. Hiccup, shivering, and coughing were noted in patients who displayed such reactions on previous treatments. One instance of excitement was noted in a patient who also showed excitement with thiopental. There were in this series five other patients who had shown severe excitement, pre or post convulsive, with thiobarbiturates but did not display this with Methohexital. In previous use of thiobarbiturates in electrocerebral therapies instances of emesis, laryngospasm, prolonged apnea, were rare but no instances of these complications were noted with Methohexital in this series. No myoclonic manifestations were noted in this series. No untoward respiratory, cardiac or gastro-intestinal features were noted in any of the patients treated.

The use of Methohexital in Nasopharyngeal electrostimulation (Nasopharyngeal-bioccipital PEC) was found to be quite satisfactory if rapid induction was done with the 165 mg. dose and then followed by another 165 mg. given slowly as the treatment was administered.

Discussion

The almost traditional use of intravenous thiobarbiturates for anesthetic procedures, specifically for pre-ECT, over a goodly number of years may not be overlooked. The features of relative safety and efficiency of administration need not be detailed again herein. The two given reasons why a new, different type of intravenous barbiturate should be presented for use in ECT and its modalities seemed to have been fulfilled in this work. To personnel accustomed to the use of thiobarbiturates and longer acting anesthetic agents the ultrashort action of Methohexital may be startling. In the former instance patients would sleep for ten to thirty minutes after treatments and one could treat others in turn. In the use of Methohexital patients may waken rapidly, suddenly, sometimes less than five minutes after treatments and then attempt or insist on getting out of bed. Precautionary preparation for this occurrence such as standing by for several minutes until practically full awakening is necessary. Then, it was noted, the rapid clearness and steadiness of movements were welcomed by the patients. This rapid awakening was thus found to get patients home or to work following treatments in half the time noted with other anesthetic agents. In using Methohexital for electrocoma and electronarcosis, wherein convulsive reactions and then electrotonus induced, the patients would frequently be at least partially awake at the termination of treatments and several minutes thereafter be ready to get out of bed.

The second reason for introducing an ultrashort intravenous barbiturate becomes apparent. The previous workers referred to indicated that Methohexital was rapidly metabolized and that there was 40% of the drug in the blood stream in three hours as compared with 60-80% of thiobarbiturates—and this was after three hour periods of anesthetic administration. In twenty-four hours following such anesthesia no trace of Methohexital could be detected as compared to as much as 35% of thiobarbiturates still in the tissues. This relative lack of cumulative effects plus the rapid awakening would enable workers in the field of electrotherapies to more clearly evaluate the intrinsic effects of electro-modalities with as little barbiturate effect as possible. In the use of Methohexital in non-convulsive stimulation of the brain stem (Nasopharyngeal - Bioccipital Technique[6]) this particular, lesser, barbiturate effect was noteworthy. Not only was the patient close to waking at the end of a three to five minute treatment period but, it was possible to do such a treatment with the patient much less deeply anesthetized throughout. And, it is quite likely that practically all other modalities of non-convulsive electrotherapies could be administered by means of such "lighter," intermittent anesthesia.

A common finding in the routine use of thiobarbiturates is the occurrence of an unpleasant smell-taste experience, described as "sulfurous," "oniony." On repeated administration such an unpleasant gustatory reaction is impressive enough to make the patient discontinue treatments and even forms somewhat of an aura of unpleasant recall perhaps many months after treatments have been discontinued. Experiences of this type have not been noted in the use of Methohexital.

A final note in discussing the use of this anesthetic agent is offered. Admittedly, it may be partially conjectural and concerns the possible use of Methohexital in narcosynthetic or narcoanalytic procedures. Aside from the described rapidity of metabolising and thus awakening there is the possibility of a central stimulating action. The original isomers of Methohexital to be used in anesthetic work were found to produce preconvulsive myoclonic movements in presumably normal patients.[5] This was further verified in EEG studies, including my own to be published later. The possibilities then, of an ultra-short acting analeptic-anesthetic agent warrants serious investigation for therapeutic implications as well as for neurologic diagnosis.

All articulate patients were questioned as to difficulties in subjective reactions to Methohexital and previously employed thiobarbiturates in electrocerebral therapies. For the most part, the rapidity of action and rapidity of awakening was commented upon favorably in retrospect. The reaction immediately upon awakening from treatments was one of urgency to get up in most in-

stances. The relatives waiting for the patients would at first question if the patient has "slept enough." Then the rapidity of sensorial clearing was welcomed—in comparison to waiting for 1-2 hours before the patient was able to leave. For the ECT types of treatments with the Reiter Apparatus (#SOS-656) it was found that an unusually brief administrative routine developed that was duplicated several hundred times: Methohexital (165 mg.)—atropine (gr. 1/100)—succinylcholine (25 mg.) solution injection—10 seconds; maximum convulsant stimulation—5 seconds; tonus-clonus—20 seconds; spontaneous respiration at 50-60 seconds; awake at 3-5 minutes; out-of-office at 15 minutes. At any rate, the intermediate metabolites of both Methohexital and its isomers may have further importance in neuropsychiatry.

Conclusions

1. Methohexital was used as an intravenous anesthetic agent for electroconvulsive, non-convulsive and electrocoma therapies in 696 trials in 72 patients.

2. The anesthetic efficiency, safety, rare incidence of complications and ease of administration compared favorably with the commonly used thiobarbiturates.

3. The duration of anesthesia in electrocerebral procedures was considerably shorter than noted with thiobarbiturates. Treated patients could return to work or home in about half the time noted with other barbiturates. This ultrashort action was felt to have distinct importance in separating electrostimulative from barbiturate effects in the treatment program.

4. Methohexital warrants serious attention as an anesthetic agent in electrocerebral therapies.

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497 State Street, Albany, N. Y.

Author's Note: Methohexital used in this study was supplied through the Eli Lilly Research Laboratories, Indianapolis, Indiana.

Some of the patients were treated at Marshall's Sanitarium, Troy, New York.

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Succinylcholine Modified EST

JAMES E. RAPPA, M.D.

Modifications of all phases of electroshock technique have been developing ever since the first application of electroshock treatment by Cerletti and Bini. There have been changes in the type of current ranging from crude alternating current to the various modifications of current presently employed. Variations of the time factor with the stress being placed on increasing duration of the applied current is gaining in vogue. Later changes were made along the lines of modifying the type of current being administered from the original 60 second cycle alternating current through the differential cerebral stimulation as advocated by Lieberson, down to the most recent unidirectional direct type of current recommended by Reiter. Other modifications have been the "glissando technique," the petit-mal grand-mal technique of Impastato, the spread convulsive techniques, and others.

Other phases of the treatment have also undergone changes; such as, in the use of anesthesia, muscle relaxants, oxygen, pre and post convulsively, and the administration of supportive measures.

The purpose of this presentation is to demonstrate still another modification of treatment, one utilizing the Reiter unidirectional current without anesthetic with small dosage (10 mgs.) of a muscle relaxant, succinylcholine chloride (SCC). The objective of this procedure is to administer a grand-mal, but avoiding the dangers inherent in the use of a barbiturate anesthetic.

In our demonstration the first patient will receive unmodified treatment utilizing straight application of unidirectional current without any pre-medication. It is noted that this patient sustained a moderately severe initial tonic seizure, yet without any gross large muscle movement involving either the extremities or the back, and that the clonic phase was suppressed throughout the treatment phase by the maintenance of a current level of between 15 and 20 milli amperes. At the termination of the clonic phase (approximately 45 seconds), the patient went immediately into a flaccid state and started spontaneous breathing within a matter of a few (approximately 10) seconds.

In the second case 10 mgs. of SCC were given intravenously and upon indication by the patient of subjective reaction to the muscle relaxant (usually a statement by the patient, "I feel something," or a facial expression indicating the beginning of the action of the relaxant), the current was administered in its usual form. It was then instantaneously raised to the point of "flaring" of the feet indicating the occurrence of a grand-mal. From here on the procedure was as described above, mainly suppression of the clonic phase by the continuing administration of the current at an optimum level (usually 15 to 20 m.a.), and then reduced either to zero or to approximately 2 m.a., in order to stimulate breathing. The seizure in this case, because of the muscle relaxant, was noticeably softer than in the first patient.

Summary and Conclusions

Two patients received electroconvulsive treatment. The first patient had the usual treatment without modification and the quality of the seizure was more severe than in the second patient receiving a modified technique recommended by Impastato, namely 10 mgs. of SCC followed by standard unidirectional current treatment. The second patient had a softening of the seizure. It is felt that the 10 mg. SCC technique is a considerable advance in the effort to further minimize the risk of shock treatment, eliminating those complications occurring with the use of a barbiturate anesthetic, without sacrificing the desirable effects of a muscle relaxant.

New Aid to Neurology: Measurements with Calibrated Sedac

SAUL I. HELLER, M.D., and REUBEN REITER, SC.D.

Measurement of paralyzed muscles and nerves may be made by a skillful, experienced specialist with established techniques of galvanic and faradic currents. However, these techniques are relatively crude, and even in skilled hands accuracy in diagnosis is considerably less than 100 per cent. To overcome this difficulty Lapicque and Bourgignon developed the methods and techniques of measurement known as Chronaxie. This method, while an improvement, still had two basic deficiencies. Difficulty in accurately locating the point of stimulation so that the measurement is reproducible, and the problem inherent in using an atlas of the body to find the relative Chronaxie time for each point of the body. The difficulties inherent in Chronaxie measurements were in part resolved by a technique developed by Wilcox and Reiter working with Resnik in Boston and named Electronaxie (presented but not published). The latter technique disposed of the need for a body atlas of measurements with locations and made use of the basic intrinsic excitability constant of the neuronal structure independent of location. However, even Electronaxie required extreme care in locating the point for stimulation. For this reason, it was felt that it would not attain any greater popular use than Chronaxie.

These muscle-nerve measurement problems have been avoided in large measure by the development of the calibrated Reiter Model SOS Sedac-Stimulator. This provides electrical stimulation over a large range of intensity below the patient's pain threshold. It has been possible to calibrate this range in three discreet scales running from zero to 10, 100 and 1,000. Within these ranges we are able to measure minimum sensitivity and maximum tolerance.

This method of measurement is similar to standard test procedures in neurology. For example, in testing the Babinski or abdominal reflex, we make use of a reflex arc; we stimulate the sole of the foot or the abdomen so that the nervous system carries a message along the periphery to the C.N.S. where information is accepted, interpreted, and an answer returned which we observe as a neurological sign. In the same way, we use our Sedac current to stimulate so that information is transmitted to the C.N.S. and the answer is returned in the form of a sensation reported by the patient. In each case the C.N.S. serves as a machine for accepting information and sending back the answer. We need only interpret the meaning of the answer. Fortunately the interpretation is not difficult since the intensity of stimulus is definitely correlated with the degree of responsiveness. The higher the stimulus required, the less responsive or alive is the pathway being stimulated. Likewise, the lower the stimulus required, the more responsive or alive is the pathway being stimulated. The following is an illustrative case.

A young woman of 32, married, mother of several children, had attempted suicide by leaping from a window. She fractured her left femur, which was driven into the pelvis. The sacrum was crushed and she developed complete foot drop with paralysis of the quadriceps and some weakness of the gastrocnemius and psoas muscles. Although convulsive treatment quickly relieved the depression, her injuries impaired her ability to walk. At the time of our measurement one and one-half months had already elapsed since the injury. There had been no improvement in her neurologic condition. We measured at the injured motor points to determine degree of responsiveness or lack of responsiveness. This enabled us to initiate stimulatory treatment at intensity levels within the measured values at physiologic levels most propitious for recovery of muscle function. Following treatment our patient had improved enough to climb stairs. Initial measurements were taken at the motor points using an indifferent cuff electrode applied to the right ankle, and an active electrode applied in turn at each of the following three motor points:

1. Right thigh quadriceps.
2. Right anterior tibial.
3. Right toe extensor muscles.

The Sedac current used for measurement and treatment is described in a separate paper which develops the theory of these currents from basic concepts and describes the type of current. To avoid duplication and complexity, we should like to add here that the Sedac currents are of high frequency in

the 1,000,000 cycle range and that they consist of a complex group of high frequency current components added together. They have the important advantage that they are capable of stimulating both sensory and motor response while remaining under the "cut-off" of pain threshold. Furthermore, we have been able to calibrate the intensities in the useful ranges in accordance with the logarithmic laws of physiological response which are described in standard texts in psychology as the Weber-Fechner law. In simple terms, this law states that the stimulus increase required to produce a discernible sensation increase maintains a ratio constant to the total stimulus. In the field of hearing, calibration of intensity has been accomplished using decibels as the convenient units of measurements. In our work we have likewise set up a practical and convenient unit of intensity which we call the Sedac unit. Thus we substitute a convenient, practical unit for a complex mathematical formulation of many frequencies at various intensities. The principle we have followed is similar to that used by the definers of the Roentgen unit to describe the complex formulation of an x-ray beam.

Returning to our method of measurement in the above case, we measured the initial minimum sensitivity and maximum tolerance in Sedac units at each of the three motor points. Then we continued to measure the maximum tolerance in Sedac units at the same three motor points at different times in order to establish the dynamics of responsiveness at that particular motor point. The dynamic curves of responsiveness for these motor points have been plotted in a graph (Figure 1). Note that on the lowest curve the maximum tolerance is lowest and rapidly diminishes with time to indicate normalization or improvement. On the middle curves the maximum tolerated intensity is higher and remains constant with elapsing time after the initial changes so that it is evident the degree of trauma is relatively great. Finally, at Point 3 the patient has maximum tolerance of very high order, and as the stimulus continues with elapsing time, the patient's tolerance increases, so that it is evident that the degree of trauma is high and unstable in a worsening direction. In treating this patient with the Sedac as a therapeutic measure we use as much current as a patient finds comfortable, as indicated in the lower two curves, and record the changes toward lower intensity with respect to elapsed time. However, the top curve calls for more careful attention, and we apply the stimulus for very short periods of time with long intervals in between until the upward increase with respect to time is reduced and reversed. These three curves illustrate the three main possible conditions we may find, and the methods of stimulating therapeutically, that are as follows:

With the lowest curve we find a relatively small degree of injury or unresponsiveness measuring 340 units which continues to improve during stimulation as evidenced by the normalization, or drop, in maximum tolerance reported by the patient, till it decreases to 240 units. With the middle curve the nervous structure is initially unstable, so that during the first two minutes the tolerable intensity is not only higher than in the lowest curve, but even increases at first before returning and maintaining a constant level at 390 units. Injury or unresponsiveness is greater than in the lower curve, and shows no tendency to improve with continued stimulation over a short time. With the upper curve, the initial measurement is extremely high, starting at 630 units and dropping to 590 within the first quarter of a minute, but from then on increasing steadily over a period of 8½ minutes to indicate reduction in normal function. Unresponsiveness here is distinctly greater than shown in either of the other two curves. That the measurement is high initially and that it gets worse as stimulus is continued, are disturbing with respect to poor prognosis. In the past we have found it possible to treat such unstable situations by stimulating for a short time with intervals of rest until improvement is shown by a drop in the tolerance. Our results indicate we have a valuable new tool for determining the extent and degree of neurological injury and the dynamics of the response which indicate the future course.

To illustrate the utility of our method of measurement and treatment, we present the following case:

A young woman of 26 developed a partial paralysis of the left side of the body following a C.N.S. infection which apparently originated in an infectious sore throat. We chose to measure at the angle of the jaw on the left side of the face, and found that the patient could barely sense the stimulus when we raised the intensity to 2.3 units and tolerated as much as 44 units before reaching maximum tolerable pain threshold. We next stimulated on the opposite or right side until the patient barely sensed the stimulus, and observed a relatively large amount of muscle motor response. Since the muscle motor response with the minimum discernible stimulus was much greater than on the paralyzed left side, we assumed that the right side was receiving a greater intensity to cause this motor response. However, this judgment proved wrong, since the measurement indicated almost exactly the same intensity, 2.4 units.

This case illustrates the objective value of the actual Sedac measurements expressed in units as opposed to purely observational methods. Moreover, the maximum tolerable stimulus was soon reached at 12 units on the good side. It was reassuring to realize that sensitivity was almost equal on both the paralyzed and normal sides, even though the maximum tolerable stimulus on the paralyzed or injured left side was more than three times greater. It was also reassuring to note that the patient had recovered considerable sensation and motor responsiveness on the injured left side at the end of these few minutes of stimulation, during which we made our measurements.

Patients consistently report that the stimulation restores motor function rapidly and that they are greatly relieved to find this return of function occurring quickly. In every case the smiles and feeling of well being are evidence of the psychological advantage accompanying the stimulation. For this reason, we feel that stimulation should be administered as soon and as often as possible after trauma has occurred.

Furthermore, we have found that in many instances stimulation is beneficial long after one would expect good results because of the lapse of time since the trauma occurred. For example, an elderly woman suffered partial facial paralysis following surgery for removal of a tumor. At the end of two years all branches of the facial nerve were barely active. Although we expected very little from stimulation after such a long time, we were pleased to find that it was beneficial at a slow, but sustained rate, so that the patient gradually began to recover motor response. Because of this success, we have now undertaken to work on another patient with complete facial paralysis of the left side of seven years duration. We hope to report on this but we already have measured and observed some improvement after a few treatments.

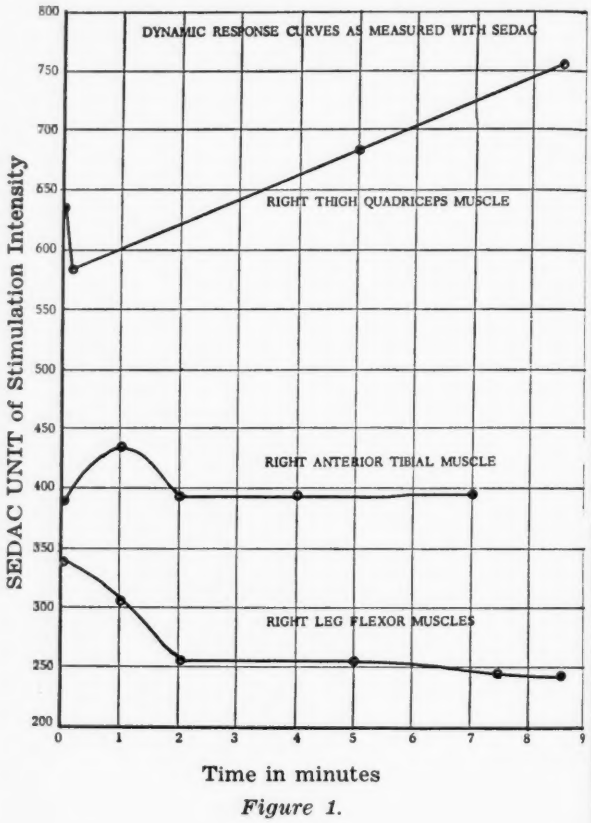

Figure 1.

Conclusion

We feel that we have a useful new tool in our possession. It is not only valuable for measurement of degree of injury and prognosis but also to treat effectively. All this is possible because the stimulus is efficient and provides strong stimulation before attaining maximum pain threshold. Added to this is the value of the calibration which permits us to determine actual measurements at all times. We can foresee valuable research possible through this method of investigation. Many investigators are already using these procedures in connection with their psychiatric treatment procedures.

High Frequency Electric Currents (Sedac) for Brain Measurements, Diagnosis, Therapy

ALFRED E. EYRES, M.D., JOSEPHINE KNIGHT and
REUBEN REITER, SC.D.

This project originated nearly three years ago. Its inception is based upon the logical and pressing need for a method of measurement applicable to neurological or psychiatric problems. With such a means of measurement, it becomes possible to more accurately determine the site of the illness, and to correlate accurately measured progress with clinical progress. We have been gratified to find that such a correlation does exist and we present some of our findings in this paper. Further, more detailed elaboration will be presented in later reports.

Our work has been done with the Sedac currents of the Model SOS Reiter Sedac Stimulator. These currents consist of volleys or groups of pulses, each pulse consisting of a combination of high frequency currents of the order of one million cycles and higher frequencies. We measured 70 normal individuals to determine the average or base response found in the relatively healthy individual. We compared their responses to those found in neurologic and psychiatric patients. We found that these patients exhibited gross abnormality in measurement as compared with our normal individuals. Furthermore, stimulatory treatment at the site of abnormality led to improvement in the clinical picture as well as in the measurements that we were able to obtain following treatment. This method of measurement is not difficult to apply and may be learned by any capable person. The procedure is simple in theory and application. Forms are available which specify the location of electrodes for each measurement in numbered order and the arrangement of electrode placement seeks to avoid excessive consecutive stress in any area.

Without going into basic details any more than is necessary for this introductory paper, the technician slowly raises the intensity of the stimulus until the patient barely senses his response at the site of the electrodes. The number of stimulus units is then read off from the calibrated Sedac scale and recorded on the form chart. This measurement is made at each electrode position as listed on the chart until all of the minimum sensitivity measurements have been recorded. At this point the patient is usually most cooperative and has become completely familiar with the procedure of detecting his response accurately and quickly. It is then explained that we want to measure patient's maximum tolerance, that is the maximum amount of stimulus he can tolerate without pain. We further explain that this measurement will be accurate only if patient does not allow us to cause him any pain. Thus it is possible to record the maximum tolerances at a very rapid rate for each of the positions of the electrodes. When the measure-

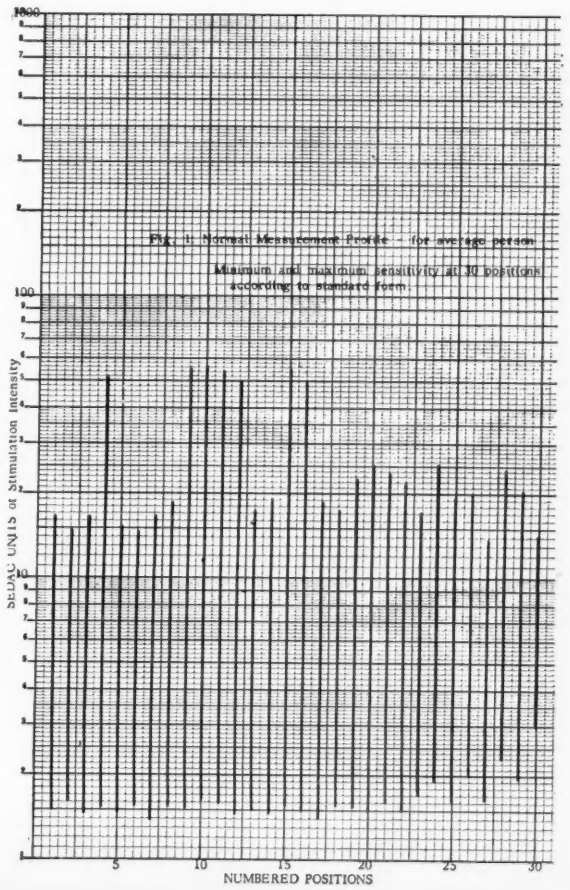

Fig. 1: Normal Measurement Profile — for average person. Minimum and maximum sensitivity at 30 positions according to standard form.

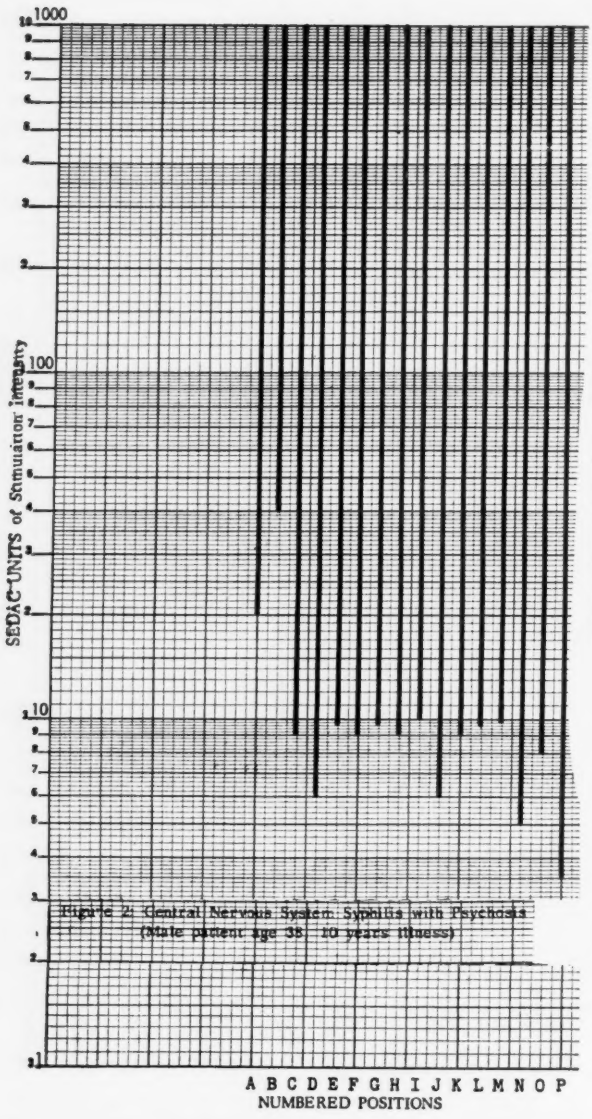

Figure 2: Central Nervous System Syphilis with Psychosis (Male patient age 38; 10 years illness)

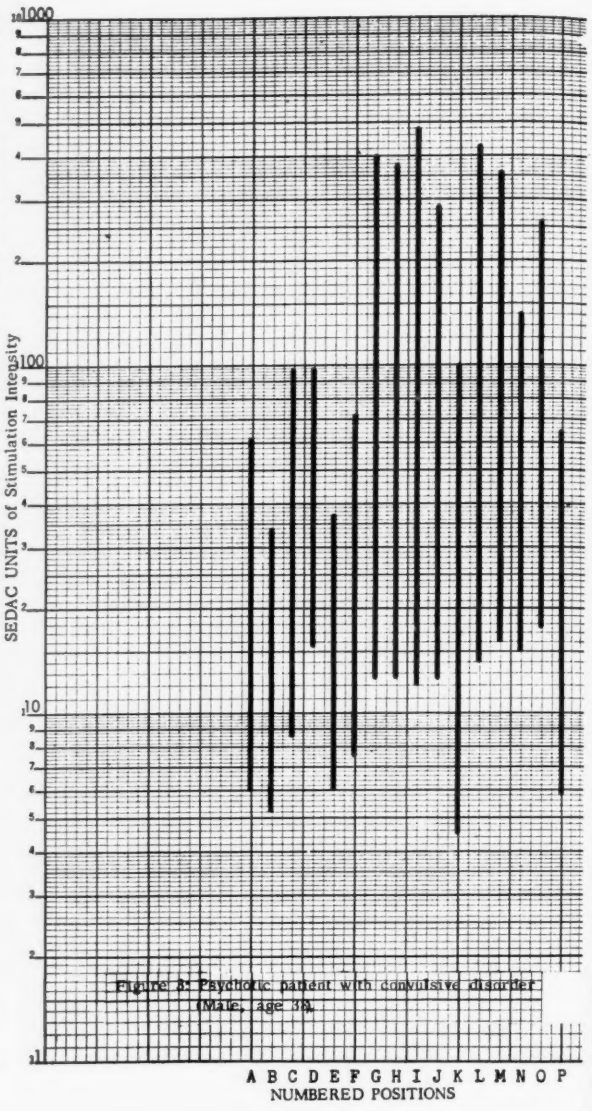

Figure 3: Psychotic patient with convulsive disorder (Male, age 38).

ments are finished, the patient feels comfortable and content at having helped to establish the entire procedure. It is a desirable form of cooperation between the patient and the doctor's staff.

It is now possible to determine the relative degree of normalcy or abnormality from the readings on the form chart, or better yet it is possible to plot the measurements on a sheet of three-cycle semi-log paper which gives a full view of the measured brain profile at a single glance. Figure 1 shows such a brain profile as plotted for one of our normal patients. At each electrode position, the minimum sensitivity is plotted as a single point, and then the maximum tolerance is plotted above it as another single point, and the line drawn between the two points establishes minimum sensitivity, maximum tolerance and the spread between the two seen quickly. When this has been carried out for each of the numbered electrode positions on the chart, we have a complete brain profile. Our interest in reading this brain profile is centered on: 1. Maximum tolerance at each position; 2. Minimum sensitivity at each position; 3. Spread between these two positions. The normal measurement will show a spread passing between the first and second cycle on the chart, while the grossly abnormal will reach well into the third cycle toward 1000 Sedac units. We have seen luetic patients withstand the full amount of the stimulus without any

difficulty. To a lesser degree this same lack of responsiveness is exhibited by neurological and psychiatric cases at the special electrode positions which are affected and which are determined by our measurements. To point up these examples, we show Figure 2, the measurements on a luetic case with obvious lack of responsiveness. In addition, Figure 3 shows an intermediate between the normal of Figure 1, and the grossly abnormal case of Figure 2. Our records contain over 2000 measurements for illustration of technical points.

On the basis of our measurements and work done to date, we have been able to establish a principle of measurement to locate the site of hypo or hyper responsiveness, so that we may treat with properly defined placement of electrodes. We have learned that it is worthwhile to devote attention to measured areas of abnormality in order to obtain maximum clinical response. Conversely, we have learned that failure to treat according to accurate measurements often fails to yield the desired clinical response. In fact, our measurements have demonstrated that treating at a site which is normal either yields nothing, or sometimes leads to impairment of other sites where reasonably normal measurements were previously taken. In addition, we have verified the fact that clinical improvement is usually coincident with improvement of measurement. Having determined the electrode position at which we wish to give treatment, we can give a mild treatment by merely using the maximum tolerable or comfortable intensity acceptable to the conscious patient. This mild treatment requires nothing further in the way of drugs and it is even possible to discuss pertinent matters during treatment as the patient improves.

In those cases where we have not been able to obtain measurements prior to treatment, we make use of the insight which our measurements have already provided us. We have found that it is desirable to treat the more primitive areas of the brain. For this purpose we apply electrodes in several positions on the head and tie them together with a short circuiting, or jumper, electrode connector. Our preferred method of approach is to apply one electrode at the forehead and one each at the left and right occiput, utilizing the head band to retain them in position, and connecting with a three connector wire so that all three electrodes act as a single unit. The second unit electrode is the wrist electrode which is applied to the wrist. Thus the machine may be connected between the head and the wrist to provide current flow from several areas of the brain down through the visceral part of the brain.

The above mentioned deep Sedac techniques of treatment have been used with marked success on patients who had not responded to convulsive therapy, drugs or insulin. From our own experience we can verify the reports of other treatment centers that this deep technique of treatment is often successful in difficult "hard core" cases. Our measurement work has been carefully followed in order to make sure that future records will have a measured, scientific underpinning, so that we may have more complete and valuable insight which will allow us to provide more efficient, and more rapid therapy for each of the categories of illness treated. This directed form of record keeping and research should be far more rewarding than statistical methods of clinical research which have been followed.

Summary

We have outlined the course of nearly three years' work in measuring localized patient brain response to stimulus at various electrode sites of application. With measurements on 70 normal individuals as a base line of reference, we have found that distinct changes in responsiveness may be observed in patients with neurological or psychiatric syndromes. When Sedac treatment has been applied at the measured sites of abnormality, patient response has been gratifying even in "hard core" cases, including those who had failed to respond to other therapy.

Unidirectional Regressional Modified ECT vs. Tranquilizers in Chronic Schizophrenics

HERMAN TANOWITZ, M.D., JAMES E. RAPPA, M.D., and JOHN MARCHITELLO, M.S.

On the wards of the continuous treatment services housing the chronically ill mental patients, a newly generated spirit of optimism has burgeoned as a result of the improvements achieved with the current methods of treating schizophrenia. Whereas in the past, alternating current, ECT, insulin, metrazol, Sodium Amytal and phenobarbital were generally used to modify the psychosis, we have recently added regressional therapy, tranquillizers, group psychotherapy, socializing therapy, the open door policy and half-way houses. The acute psychoses and early schizophrenics responded favorably in a large percentage of the cases treated with the older methods. No such favorable response was obtained with the chronic schizophrenics who seemed hopelessly anchored in a mental mist that was almost impenetrable.

Purpose

The aim of the present project was to select a method of treatment especially suitable for a chronic service and one that would lead to a significant mobilization of the permanently institutionalized patients. In view of the large population in the continuous treatment services, it was considered necessary to devise a method that would be most eflective in achieving improvement, that was uncomplicated, and at the same time was able to reach as many patients as possible.

After reviewing the literature and evaluating our own experiences with the somatic and psychotherapeutic approaches, we decided on a method incorporating the initial use of modified regressional ECT, followed by a combination of tranquilizers in those cases that did not respond to the regressional ECT.

Procedure and Method

The project was started on November 7, 1956 with 16 patients ranging in age from 24 to 32 years. All had been mentally ill for at least three years and were either paranoid or catatonic schizophrenics. The simple and hebephrenic schizophrenics were excluded because of the less favorable prognoses with all methods of treatment. The subjects chosen were at least of normal intelligence and had been apparently mentally adequate up to the time of the onset of symptoms. Following their breakdowns they had received a variety of treatments varying from insulin, metrazol, ECT, including some form of psychotherapy. Many had more than one course of the somatotherapies but had failed to respond favorably.

After a period of psychiatric and psychological testing a prolonged study of the methods used was contemplated in order to investigate duration and reliability of the results. Too often in the past, premature curtailment of related studies had produced confusion and uncertainty regarding the effectiveness of previous methods. Too little has been accomplished in the synthesis of an acceptable approach in the treatment of the chronic schizophrenic in large continuous service centers. It is hoped that our observations would contribute to a clarification of some of the difficulties and will suggest a procedure of feasible treatment especially in the large, continuous services of mental institutions.

During the course of the procedure the patients were examined and evaluated by (1) Psychiatrists for background, diagnosis, prognosis, symptom complexes and suitability for the intensive therapies. All patients had to be physically qualified and free of any previous morbidity that might complicate the observations. (2) Psychological ratings were administered at regular intervals. Progress was plotted and charted according to symptom variability and mobility of the total personality. A schema for that purpose was devised detailing various emotional and mental traits. The patients receiving tranquilizers were evaluated twice weekly according to the above schema. In this manner, we were able to estimate the effect of the procedures on various areas of

the personality. (3) Conferences were conducted weekly with ward personnel and qualified individual attendants were familiarized with the background and mental attitudes of the patients and assigned to their care. (4) All patients participated in 3 group psychotherapy and interview sessions weekly. (5) Occupational therapy was also given every morning. Progress of patients was discussed with occupational therapy workers and emphasis was placed on observable signs of change encompassing reality contact, psychomotor activity, attention span, preferential occupations, muscular coordination, symbolic interpretation of activity and mood tendencies.

The 16 male patients were divided into two equal groups, one to be experimental and the other serving as a control. Each patient of the experimental group was given three modified electroconvulsions at intervals of one half hour (using unidirectional current of Reiter apparatus CW47C). Atropine sulphate 1/75th of a grain was given subcutaneously 45 minutes before each treatment. The first convulsion was preceded by an injection of 5% thiamylal (Surital) intravenously, sufficient to induce light sleep. The dosage varied from 100-450 mg., each patient usually required approximately the same amount of Surital in the treatments of the following days. An amount of succinylcholine chloride equal to 40 mg. was then injected rapidly through the same needle. After a period of 15-30 seconds, generalized fasciculations were observed, followed by a rapidly spreading muscular relaxation. At this time, after the insertion of an airway, the patient was respirated using 100% oxygen. The electroconvulsion was given 60 seconds after the succinylcholine chloride. For the second and third convulsions which followed at ½ hour intervals a different method was employed. The Surital was eliminated and the petit mal-grand mal method described by Impastato was utilized. The amount of succinylcholine chloride injected was reduced to 20 mg. At the termination of each convulsion, the patient was oxygenated with 100% positive pressure oxygen. Blood pressure, pulse and respiratory reactions were recorded before and after each convulsion. Hyperextension and restraint of patient during the convulsion was not necessary. An airway was inserted routinely after each convulsion and when indicated.

With the above method, intense cyanosis was rare and mild cyanosis infrequent during all three convulsions. Apnea rarely lasted for more than two minutes and never created any complications of consequence which was especially gratifying. The evaluation of muscular relaxation was related to a schema previously used and the response varied from slightly reduced to definitely reduced, the latter occurring regularly in six of the patients. The eight patients of the experimental group received a total of 36 convulsions during a period of two weeks. The Sunday between the two weeks was used as a rest day. After completion of the regressional ECT the patients were thoroughly examined for physical and mental changes and then started on the important adjunctive rehabilitative functions, such as individual and group psychotherapy. Occupational, recreational and socializing therapies were also intensely applied. The control group received identical attention and management so that a definite correlation of approach existed between the two groups. Great care was taken to create as favorable an environment as possible in promoting desirable personality changes and mental growth. This procedure was conducted over a period of 17 months and 26 days, a period of time thought to be sufficient to properly evaluate both the short and long term efficacy of the method.

Combined Drug Therapy

Combined drug therapy was instituted on April 3, 1958, and was given to both the experimental and control groups. Blood and urine studies were performed on all patients before therapy and thereafter at intervals of four weeks. The concomitant adjunctive therapies identical with the procedures previously described were continued. A combination of three tranquilizers was administered orally consisting of perphenazine (Trilafon) 8 mg., Serpasil 0.25 mg. and meprobamate (Equanil) 400 mg. four times daily. The dosage was kept constant for the purpose of equating the effect on individual patients as well as to study the possibility of evolving a combination of drugs that would

be effective in the treatment of the chronic patient. No other drugs were used except anti-parkinsonian drugs to counteract basal ganglion symptoms.

Results and Comment

The eight patients receiving modified regressional ECT with unidirectional current (Reiter apparatus) and intravenous Surital and succinylcholine chloride were amazingly free of complications. Apnea was minimal, and ranged from 30 seconds to two minutes. Although no EKG's were taken during the treatment, clinical examination of the cardiovascular system showed infrequent occurrence of cardiac arrythmias. There appeared to be a greater frequency of pulse irregularities with the petit mal-grand mal method than with the Surital-Anectine method. There were no irreversible changes and all arrythmias disappeared approximately 3-5 minutes after each convulsion. Blood pressure showed the usual increase after ECT but remained much lower than with the unmodified ECT methods. Blood pressure continued to rise as the treatment progressed and after approximately the 12th convulsion attained a new high usually averaging about 10-20 mm. of increased systolic blood pressure. The diastolic blood pressure appeared to parallel the systolic. In two patients the blood pressure and pulse remained fairly constant and responded with only slight increases. When the blood pressure and pulse rose sharply, there occurred a subsequent fall in blood pressure and a slowing of the pulse. The mechanism suggested in explanation of the above is as follows: A relative increase in blood pressure and heart rate occurs after an electroshock treatment. The aortic and carotid depressor mechanisms (vagal pathways) are then stimulated resulting in hypotension, bradycardia and cardiac arrythmias. Satisfactory atropinazation usually is effective in modifying these vagal effects. Mental confusion appeared approximately after the sixth convulsion and the secondary symptoms of schizophrenia began to visibly subside after approximately the ninth convulsion given on the third day of treatment. Marked regression occurred on the sixth treatment day; three patients began to wet and soil, two had to be tubefed and six spoonfed. Ten days after completion of the regressional ECT all patients had recovered their ability to care for themselves, eat properly, and were able to respond adequately to the therapies that had been prescribed.

All patients improved noticeably. Five were greatly improved and three moderately. The improvement consisted primarily of the development of greater contact with reality, increased perceptiveness, better muscular coordination, removal of depressive elements, reduction of agitation and excitement and total or partial elimination of hallucinatory phenomena. Paranoid ideas, although not as pronounced as before treatment, were discernible by the continuing existence of projection systems. Grasp, retentive and discriminative faculties showed considerable elevation of functional capacity. The ability to recall past and recent events climbed steeply following recovery from the confusional state. (It is noteworthy that memory acuity was retained notwithstanding an almost complete retrogression of all other faculties to the previous psychotic state.) The mental condition of the patients began to deteriorate clinically at approximately the beginning of the third month after conclusion of the regressional treatment and continued progressively until the sixth month when there was almost a complete return to their previous psychotic constellation. The intensive rehabilitative therapies continued but were ineffective in restoring any of the gains previously achieved. In view of the lack of response of the chronic schizophrenic to regressional ECT and the concurrently administered adjunctive therapies, it is apparent that other avenues of approach should be investigated. In this connection a number of tranquilizers were evaluated both separately and in combination.

A combination of perphenazine, Serpasil and meprobamate, exhibited distinct advantages in its rapidity of action and in its ability to control symptoms of hyperactivity.

The 16 patients representing both experimental and control group received the above combination of tranquilizers and reacted favorably after only two or three days. The total response of the patient apparently reflected the properties of the individual drugs.

It appears that this combination of tranquilizers has a broad range of effectiveness and is to be preferred as the initial and immediate therapy in the chronic schizophrenic. All 16 patients are at the present time greatly improved mentally, and have, to a large extent, resumed contact with their surroundings. Especially noteworthy was the excellent response to the medication of the two previously most regressed patients in the group. These patients were almost completely disorganized mentally, exhibited assaultive behavior and had been confined to a disturbed ward. Although not completely recovered, these two patients have improved to such an extent that they are now able to participate in all of the therapy sessions, reside on an open ward and are permitted home visits.

The side effects of the tranquilizers have been minimal. Three patients complained of nasal congestion and drowsiness, one patient developed a punctate, pinkish rash confined to the upper anterior chest region. Hypotension did not occur although there was some lowering of the systolic blood pressure in four. Parkinsonism appeared in six cases but was easily controlled with anti-parkinsonian drugs (Pagitane). There have been no blood dyscrasias or hepatic disabilities. The response of the patients to the combined tranquilizers has been most gratifying. The drugs used were selected for their specific actions and low toxicity reactions. Perphenazine has been especially valuable in this respect, due to its high therapeutic ratio and low dosage required for effectiveness.

Psychological Evaluation of Regressional ECT

In past studies of the psychological effects of ECT, it has been reported at different times that it produces confusion and disturbance of memory functions in patients,[4,5,6] and then again others claim that mental efficiency is improved beyond that of the pre-shock level.[9,12]

In part, the differing clinical results would appear to be a function of the kinds of procedures which are employed. For example, there is a significant variation in results[6] depending on whether unidirectional current is applied with the Reiter machine, or sine-wave alternating current is delivered with the conventional apparatus. This study made use of the Reiter's unidirectional current in a regressional form of ECT.

The 16 chronic adult male schizophrenics sampled for the study had not shown improvement after previous somatic treatments and had displayed marked regression.

Before treatment, all subjects were administered the following test battery.

1. Wechsler Memory Scale, Form I.
2. Word Associations.
3. Bender-Gestalt Visual-Motor test.
4. Szondi test.
5. Lowenfeld Mosaics test.

The two groups of eight each were equated on the basis of the following factors:

1. Age (24-32 years).
2. Nature of previous somatic treatment (drug or convulsive).
3. Length of hospitalization (8-118 months).
4. Number of previous admissions (1-3).
5. Wechsler Memory Quotient (45-99).
6. Frequency scores for 25 words of the Kent-Rosanoff Word Associations Test (8-3773).

One group served as a control group which was not subjected to regressional treatment.

Two weeks after ECT was terminated the experimental patients had recovered sufficiently from the confused, regressed state to be re-tested along with the control group, utilizing the test battery, with the sole change that the alternate form, Form II, of the Wechsler Memory Scale was given in place of Form I. One month later, both groups were begun in special occupational

TABLE 1—*Sums of Ranks and Non-Parametric Analysis of Variance of the Wechsler Memory Scale Scores for the 8 Experimental Patients.*

Wechsler Memory Scale Sub-Tests	First Testing	Second Testing	Third Testing	Fourth Testing	X^2r
Personal Information	16.5	17.0	21.0	25.5	3.98
Orientation	17.0	19.0	21.5	22.5	1.39
Mental Control	21.0	18.0	18.5	22.5	1.01
Logical Memory	18.0	17.0	23.0	22.0	1.95
Digits	16.0	17.5	25.0	21.5	3.71
Visual Reproduction	15.0	18.5	26.0	20.5	4.76
Associate Learning	12.5	18.5	29.0	20.0	10.46*
Memory Quotient	13.0	15.0	28.0	24.0	11.55†

*Significant at .012 level.
†Significant at .009 level.

therapy and psychotherapy programs still in progress.

This study further differs from other investigations, especially those finding only post-shock confusion, in that follow-up testing was done at extended intervals after the ECT. A second retesting (using Form I of the W.M.S.) was administered 22 weeks after the treatment, and a third re-testing (using Form II) was done fully 64 weeks after the regressional ECT.

In Table I the Wechsler Memory Scale scores for the experimental group are shown by sums of ranks and analysis of variance,[15] to change significantly with respect to the memory quotients and the associate learning sub-test scores. The change in associate learning is significant at the .012 level and the change in memory quotients is significant at the .009 level of confidence. The rise in scores for the group is highest in the third testing, five months after the shock treatment, and part of the rise is sustained in the fourth testing, more than a year after the ECT.

TABLE 2—*Sums of Ranks and Non-Parametric Analysis of Variance of the Wechsler Memory Scale Scores for the 8 Control Patients.*

Wechsler Memory Scale Sub-Tests	First Testing	Second Testing	Third Testing	Fourth Testing	X^2r
Personal Information	22.0	24.5	17.5	16.0	3.49
Orientation	20.5	19.0	18.5	22.0	.56
Mental Control	20.5	17.5	24.5	17.5	2.48
Logical Memory	20.0	14.5	23.0	22.5	3.41
Digits	23.0	16.0	20.0	21.0	1.95
Visual Reproduction ..	18.5	24.5	16.0	21.0	2.96
Associate Learning	20.5	12.5	26.0	21.0	4.99
Memory Quotient	17.5	14.5	22.0	26.0	5.74

In Table 2 is shown the control group's Wechsler memory quotient and associate learning scores which do not vary significantly through the same four testing intervals. In none of the other subtests of personal information, orientation, mental control, logical memory, digits and visual reproduction do the results vary significantly for either group.

Mean Wechsler Memory Scale Quotients of Control and Experimental Groups for the Four Test Intervals

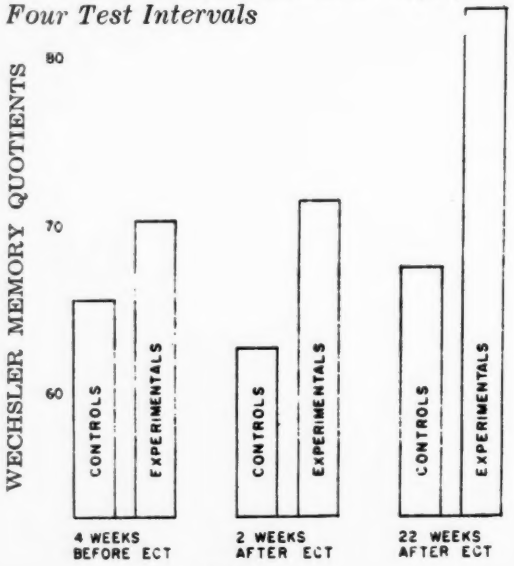

Figure 1.

In Figure 1 there is a graphic comparison of the mean memory quotients for the control group and the experimental group. The differences between the groups is not significant[11] in the first testing (the pre-shock testing), nor in the first and last post-shock tests. In the third test interval, however, the difference in favor of the experimental group is significant at the .047 level.

From these results it may be concluded that there was a delayed effect of the regressional ECT and that a significant rise in memory quotients and associate learning appears four months after ECT. This effect is diminished 64 weeks after regressional ECT is terminated.

In the next part of this study the associative function, which seemed to enter significantly into the results for the Wechsler memory scale measures, is examined more closely in the data of the word association test. A list of 49 stimulus words is used in this test. The first 25 words are taken from the Kent-Rosanoff list[10] and the remaining words are comprised of eight double-meaning words and 16 emotionally-charged words. The response words to the Kent-Rosanoff list were scored according to the Kent-Rosanoff frequency list. In principle, the frequency score depends upon how common or popular, are the responses given for the stimulus words.

Kent-Rosanoff Mean Frequency Scores for 25 Word Associations

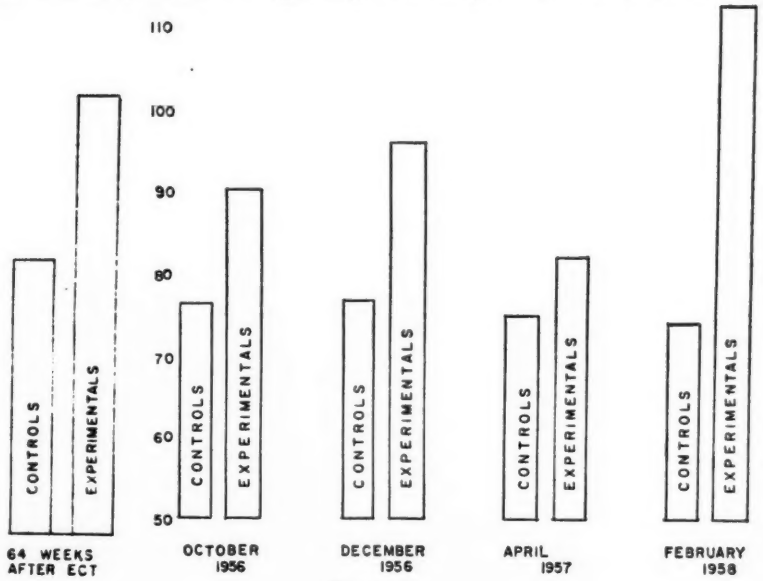

Figure 2.

Figure 2 compares the mean frequency scores for the first 25 word associations of the two groups. The control group's scores remain nearly the same in each of the four test intervals. However, those for the experimental group change significantly[15] at the .041 level of confidence. Here the highest (mean and median) score appears in the fourth testing.

From this data it may be concluded that the experimental group changed significantly in associative functioning after the regressional ECT, and their responses were most relevant and appropriate in the testing interval 64 weeks after the regressional treatment.

Reaction time data for the Kent-Rosanoff, double-meaning, and emotional words were analyzed separately, and there were no significant changes in the results for either the control group, or the experimental group.

Several projective techniques[1] were included in the test battery and these were selected because they could be scored objectively in certain respects. The Bender-Gestalt visual-motor test is based on the ability to copy a number of designs. This test was scored according to the Pascal system,[8] and again the experimental patients performed most effectively in the fourth testing. However, the change is just short of significance. The control group's scores tend to remain the same for all four testing intervals.

The Lowenfeld mosaics test[3,7,14] consists of plastic chips in five different shapes and six different colors. The subject is asked to make a design with the chips on a frame. The designs of the subjects in this study were scored only with respect to the shapes and the colors which were used. There was no significant change[15] in the use of form and color on this test for either group of patients.

The other projective technique used was the Szondi test.[2] It consists of six sets of eight photographs. Each picture is the face of a patient diagnosed in one of eight categories: homosexual, sadist, epileptic, hysteric, catatonic, paranoid, depressive and manic. From each set the subject is asked to choose two faces he likes and two faces he dislikes. There was no significant change[15] in Szondi choices for either group, over the four testings.

It was easier to observe the cognitive changes which followed administration of the ECT in the experimental patients. There were also emotional changes, but the projective data failed to indicate them. There were other indications, such as observations of the ward behavior of the patients that emotional changes were moving in a negative

direction, while part of the intellectual functioning, as indicated by the Wechsler Memory Scale and the Word Associations was enhanced following the regressional ECT.

PSYCHOLOGICAL EVALUATION OF THE COMBINED DRUG TREATMENT

Partly in hope of reversing the negative direction of emotional adjustment in the experimental group, the combined drug treatment, described was given all 16 subjects of the ECT study. Both control and experimental patients of the original study were given the tranquilizers, since the small number of the sample did not permit a division of the patients for controls in the treatment with tranquilizers.

It was also decided to evaluate possible changes at more frequent intervals than in the ECT study. In this respect the use of objective tests presents certain problems. They cannot be too frequently repeated without giving advantages to the subjects, of practice and familiarity with the tests, so that a daily, or weekly evaluation in applying such tests during a prolonged treatment would be impractical and would result in spuriously higher scores. Behavior rating scales and check lists are less reliable and more subjectively applied than standardized tests, but there is the advantage that they can be applied as often as the observer wishes to record the status of certain conditions in subjects studied, and they avoid the contaminating influence derived from practice with test material.

To observe the effects of the combined drug therapy, a check list was devised which attempted to follow changes in four areas of personality adjustment: Intellectual, Emotional, Personal, and Social. Each of the 16 patients were rated weekly in personal interviews. Since each patient was also in several group therapy sessions per week with the same observer, the sample of rated behavior included the patient's performance during the three group and one interview sessions in which he took part weekly.

Figure 3 shows the list of 17 pathological factors considered in intellectual adjustment. The graph presents the week-by-week totals of factors checked for all 16 patients. There is a nearly uninterrupted decline of pathology until the 12th week of the drug therapy, and then a rise appears to the 18th week. For particular factors the sharpest declines were sustained in depersonalization, obsessions, hallucinatory trends, illusionary

Weekly Totals of Pathological Factors in Intellectual Adjustment for 16 Chronic Schizophrenic Patients Receiving Combined Drug Therapy

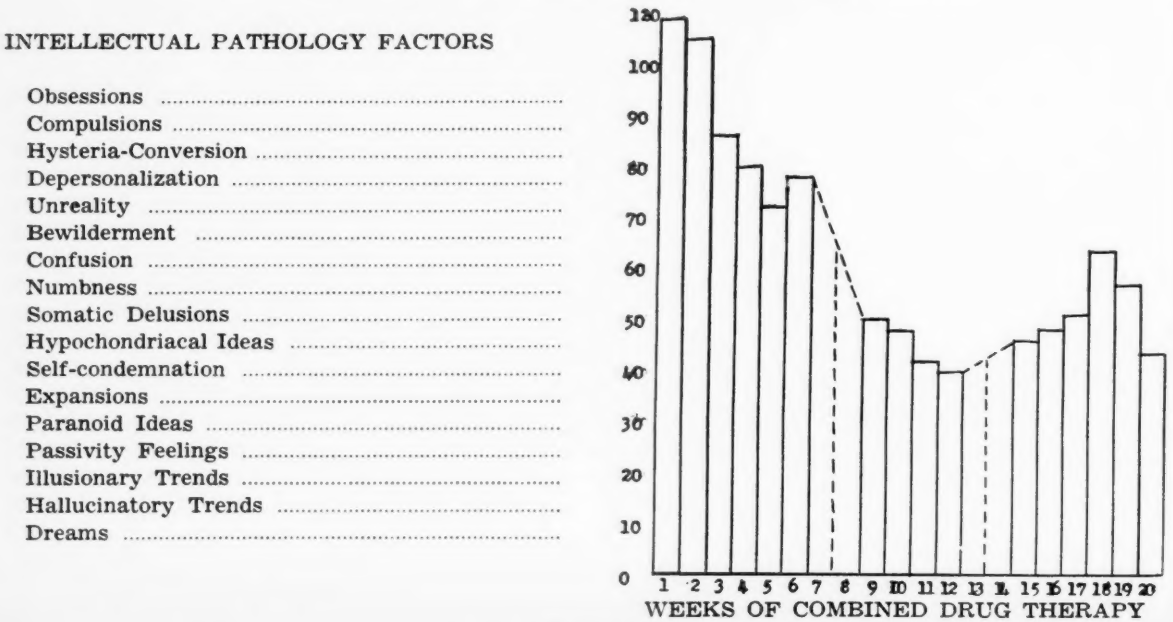

Figure 3.

trends, paranoid ideation, feelings of depersonalization and unreality.

Figure 4 lists 15 pathological factors checked for emotional adjustment. The steepest declines were sustained in impulsivity and delusions. The week-by-week totals declined in a curve similar to that for intellectual adjustment, except that the least amount of pathology is noted in the ninth to 16th week interval. The two gaps in each of these graphs are weeks in which the patients were not rated.

Figure 5 presents the list of five positive and 11 negative factors which were checked in the area of personal adjustment. There is little change in the number of adjustive traits which were observed, but there is a decline in maladaptive factors up to the tenth week, where a plateau is reached lasting up to the sixteenth week. The peak which appears for the seventeenth and eighteenth week coincides with the parkinsonian-like reactions which some patients manifested during the two-week period in which Pagitane was withdrawn.

Weekly Totals of Pathological Factors in Emotional Adjustment for 16 Chronic Schizophrenic Patients Receiving Combined Drug Therapy

EMOTIONAL PATHOLOGICAL FACTORS

- Agitated
- Irritable
- Depressed
- Retarded
- Apathetic
- Impulsive
- Delusional
- Variable
- Overactive
- Confused
- Inaccessible
- Seclusive
- Destructive
- Hallucinated
- Paranoid

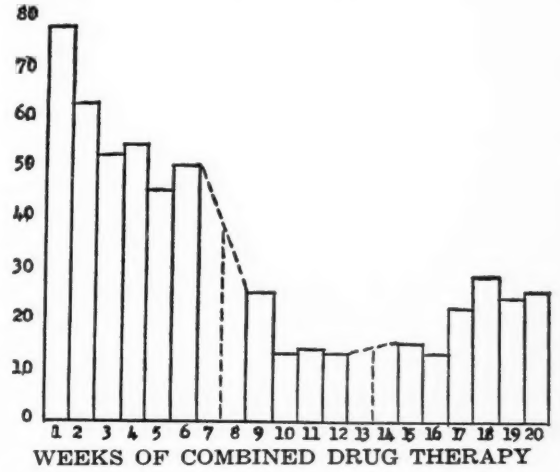

Figure 4.

Weekly Totals of Personal Adjustment Factors for 16 Chronic Schizophrenic Patients Receiving Combined Drug Therapy

PERSONAL ADJUSTIVE FACTORS

- Interested
- Industrious
- Initiative
- Competitive
- Normal Self-care

PERSONAL MALADAPTIVE FACTORS

- Over-meticulous
- Careless and Untidy
- Incontinent
- Tendency to Decorate
- Poor Posture
- Variable
- Distractible
- Indifferent
- Compulsive
- Delusional
- Fatigued

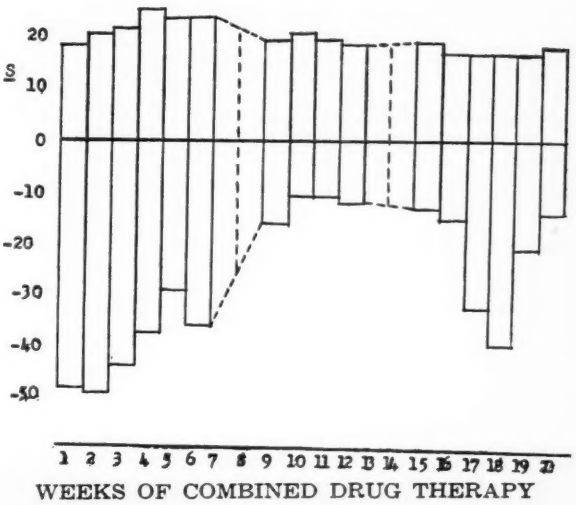

Figure 5.

Weekly Totals of Social Adjustment Factors for 16 Chronic Schizophrenic Patients Receiving Combined Drug Therapy

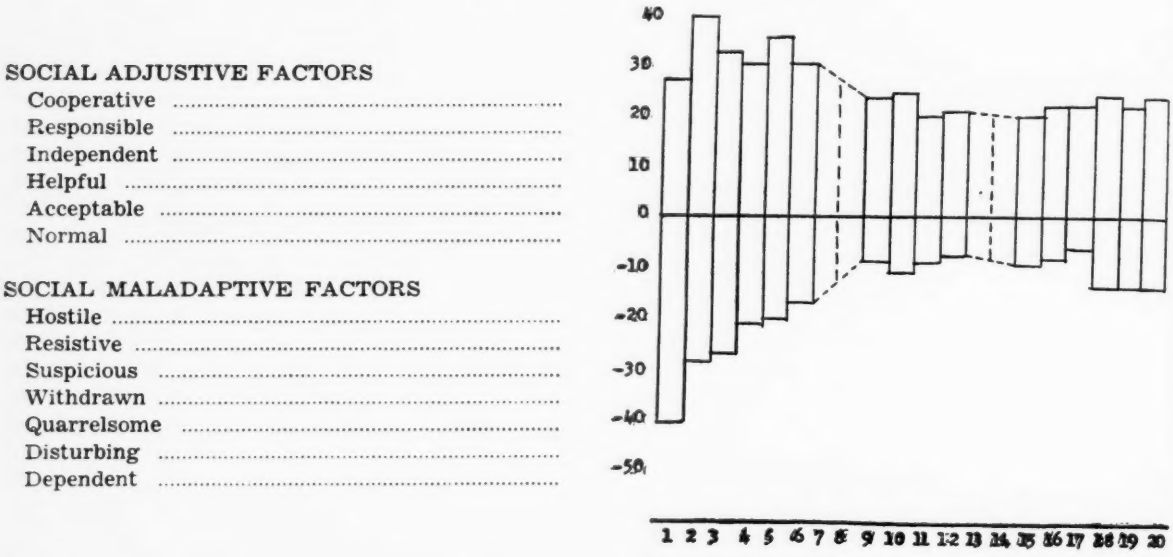

Figure 6.

The last figure reflects results similar to those in personal adjustment, for the six positive and six negative factors rated for social adjustment, except that the maladaptive totals, which also decline sharply up to the ninth week, maintain a plateau therefrom for the remaining weeks of the study.

The checklist devised to record changes affected by the combined drug therapy is certainly not the best that might be devised for this kind of observation, but it proved useful in indicating that the optimal effect of the drug treatment appears to be at about the 12th week, with no further therapeutic gains appearing beyond that interval. It also was useful in reflecting the better coordination of personality change in a positive direction during the drug treatment; whereas, after the regressional ECT, the intellectual and emotional adjustment of the patients seemed to move in opposite directions after initial improvement in both these areas.

Summary

1. Regressional ECT using unidirectional current (Reiter apparatus) and modified by thiamylal (Surital) and succinylcholine chloride, was administered to eight chronic schizophrenics. Eight similar patients were used as a control group.

2. The regressional electrotherapeutic technique was moderately effective only for a short period of time following the termination of the treatment. Mental relapse of patients began to occur after three months despite the intensive administration of individual and group psychotherapies.

3. The memory gains following regressional ECT were sustained for a greater period of time than gains of the other affected faculties.

4. Regressional ECT is too time consuming to be adopted as a routine procedure in a large hospital.

5. Seventeen months and 26 days after the regressional ECT project, both experimental and control groups were administered perphenazine 8 mg., meprobamate 400 mg. and Serpasil 0.25 mg., four times daily.

6. Good results were achieved in all patients receiving the combination of drugs. Results were particularly effective in those patients responding only minimally to the regressional ECT. Patients with tension, anxiety, agitation and hallucinations were especially benefited.

7. Side effects were minimal and when evident should be treated symptomatically. No hematologic or liver disturbances developed. Basal ganglion symptoms appeared in six patients.

8. The preferred treatment of the chronic schizophrenic appears to be a combination of perphenazine, meprobamate and Serpasil. These findings indicate that the latter combination of drugs is likely to prove more useful than previous methods in the treatment of the chronic schizophrenic. The treatment is especially adaptive and feasible for the large numbers of chronic schizophrenics in the continuous treatment services.

9. Psychologic testing was performed throughout the study at regular intervals.

10. Improvement of the patients under combined drug therapy continued steadily up to the third month at which time a plateau was reached indicating that the maximal response to the treatment had been reached. There appeared to be no further therapeutic gains after this period.

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On Mental Depressions

CARL BREITNER, M.D.

Introduction and Definition of Terms

This study attempts to promote understanding and treatment of depression. In order to discuss a topic intelligently there should be agreement as to the meaning of the concepts and terms involved. However, this does not seem to be true about manic depressive illness. Webster's dictionary defines depression in a psychopathological sense as "an abnormal state of inactivity and unpleasant emotion, as in manic-depressive insanity." Blakiston's new Gould Medical Dictionary defines depression as "an emotional state of depression usually associated with manic-depressive psychosis."

If there were no doubt about the completeness and validity of such simple definitions, the statistical and diagnostical manual of the American Psychiatric Association would not have to differentiate psychotic depressive reaction, neurotic depressive reaction and manic depressive reaction, involutional depressive reaction, schizo-affective schizophrenia, and the depressions occurring in chronic brain syndromes. The variety of depressive symptoms is further elucidated by the existence of many additional terms such as melancholia, agitated depression, reactive depression, endogenous depression, true depression, etc. By such sub-classification the idea is conveyed that a variety of depressive symptoms occurs in a multitude of different mental disorders. This is evident in reviewing the literature on the subject.

To quote: Henderson and Gillespie[1] speak of a

"... triad of symptoms: 1—Difficulty in thinking, 2—Depression, 3—Psychomotor retardation,"

and describe

"Involutional Melancholia . . . as depression without retardation, anxiety, a feeling of unreality and hypochondriacal delusions."

Leopold Bellak[2] labels depression as

"psychomotor retardation, difficulty of thinking,"

but in describing agitated depression states:

"There is emotional depression with flight of ideas and increased psychomotor activity."

Meyer-Gross[3] writes:

"The patient's sadness deepens to a morbid depression, and the difficulty in concentration becomes retardation of all thought and action . . ."

The same author on involutional depression states:

"1—Besides the profound depression, anxiety is a conspicuous element of the affective state. 2—Retardation is usually not prominent."

Arthur Noyes[4] distinguishes between mild and acute depression and depressive stupor. In speaking of severe depression he states:

"The initial downheartedness soon passes in affective distress. Posture, muscle tension and various signs and symptoms present a composite picture indicating depression. The purest type of depression is the retarded depression. In this there is inhibition of stream of thought and of psychomotor activity."

The same author, speaking about involutional melancholia (Pg. 52):

"The foundation of melancholia in this as in other depressive reactions, is to be found in a turning inward against the telf, of aggressive tendencies which can find no other outlet."

Strecker, E. A., Ebaugh, F. C., and Ewald, J. R.[5] write:

"In involutional melancholia and its sub-groups there may be a wide range of emotional reactions, including irritability, anger, inadequacy, pessimism, sarcasm, ironical witticism. The depth of the depression is shown by the frequent suicidal attempts."

Sigmund Freud[6] states:

". . . when he has a melancholic attack, his superego becomes over-severe, abuses, humiliates and ill-treats his unfortunate ego, threatens it with the severest punishment, reproaches it with long-forgotten actions. . . . The sense of inferiority and guilt are exceedingly difficult to distinguish."

It is quite obvious that the majority of authors speak of depression regardless of whether there is retardation or agitation. The only author who differentiates between true depression and conditions which are usually labeled as depressions but are really not, is Leo Alexander[7] who writes:

From Arizona State Hospital, Phoenix, Ariz.

". . . to define depression as a state of sadness with self-reproaches and psychomotor inhibition, with sleep disturbance and disturbance of appetite. Certain reactive depressions in which retardation and turning against the self in a hostile manner are absent, reveal themselves . . . to be actually anxiety states with discouragement rather than true depressions."

We learn from the above quotations and definitions that depressive symptoms, or the syndrome of depression as described in the literature, may consist of:

Psychomotor retardation		
	as well as	Agitation
State of indifference or inactivity		
	as well as	State of increased worry
State of guilt feelings and worthlessness		
	as well as	State of fault-finding, self-pity and self-centeredness

The only agreement exists on the fact that depression may lead to suicide, but suicide also occurs in schizophrenia or other psychotic reactions, for instance in toxic psychoses.

On the other hand, there is great similarity between the symptoms occurring in depression and illnesses classified under other entities such as catatonic schizophrenia. The following is a quotation from Noyes' Textbook:[4]

". . . there is practically no spontaneous motor activity. There is a complete, or almost complete, immobility with minimal response to external stimuli. The patient is mute. His sensorium is clouded, and he is intensely preoccupied, often with ideas of death and with dream-like hallucinations. Many have to be tube fed while some soil and wet themselves."

Henderson and Gillespie[1] Pg. 155, write:

". . . may be defined as a state of intensive psychic inhibition during which regression may occur to an infantile if not more primitive level. The patient usually is confined to bed, is mute, inactive and uncooperative. His bodily needs require attention in every way, he has to be fed, washed and bathed. Precautions have to be taken to prevent retention of faeces, urine and saliva. In some cases all attempts at movements are strongly resisted. In other cases the muscles are more flaccid and the body and limbs can be moulded into any position. . . ."

Most of us will agree that the picture painted in these paragraphs fits the concept of a catatonic stuporous schizophrenia rather well. However, it is interesting to note that the above descriptions are the ones of severe depressive reactions and to be found in the chapter on depressions in textbooks.

If we could give a satisfactory explanation as to the origin or etiology of the disease, the inclusion of symptoms that often appear to be the opposite from one another would not matter. We could still treat the disease as one entity etiologically. However, most of us are agreed that psychiatric treatment today is based on the observation of symptoms and since the symptoms vary, and sometimes on the surface are quite unrelated to each other, it seems reasonable that no single treatment can be the treatment of choice for all depressions. This leaves us with the question: Is it possible at all to evaluate treatment methods of the syndrome by tabulation of results with one or the other therapeutic modality? The answer is obviously no, unless we distinguish and discriminate between treatment results of one specific therapy as applied to various symptomatologies labeled as depression.

Etiology of Depressive Symptoms

In an attempt to clarify the etiology of manic depressive illness we should consider all theories advanced and plead the case for each. The aspects to be considered are: Analytic-Psychological, Anatomic-Physiologic, and Pharmacologic.

Analytical Aspects:

The psychodynamic factors advanced by analysts as etiological of depressive reactions are familiar. There seems to be agreement among analysts that a psychic trauma in early childhood can be found in all patients who develop a manic depressive illness. Sigmund Freud[8] formulates the psychopathology of depressions as follows:

". . . Mourning is regularly the reaction to the loss of a loved person or to the loss of some abstraction which has taken the place of one, such as fatherland, liberty, an ideal, and so on. As an effect of the same influences, melancholia, instead of a state of grief, develops in some people whom we consequently suspect of a morbid pathological disposition. . . . The conclusions which our theory

would require, namely, that the disposition to succumb to melancholia—or some part of it—lies in the narcissistic type of object choice. . . . The self-torments of melancholiacs, which are without doubt pleasurable, signify, just like the corresponding phenomenon in the obsessional neuroses, a gratification of sadistic tendencies and of hate, both of which relate to an object and in this way both have been turned round upon the self. . . . When mania supervenes, the ego must have surmounted the loss of the object. . . ."

Obviously it is the belief of the analytical school of thought that life experiences or environmental circumstances are the causative factors of manic depressive illness, and there seems to be little recognition of predisposing physiological or physiopathological mechanisms. However, such physiopathological mechanisms undoubtedly exist.

On the other hand, we must acknowledge that among the factors contributing to the development of mental disorder, the psychological mechanisms are still the ones that are easiest understood. This we owe to Freud and his followers.

Anatomic-Physiologic Aspects:

The case in favor of organicity is strongly presented by Kraines,[9] wro writes:

"Analysis of the anatomic and physiologic functions of the hypothalamus, thalamus, rhinencephalon and reticular formation, points strongly to their major role in the mechanism of the manic depressive illness." . . . "The cerebral cortex is always involved, secondarily, when the diencephalic area is disturbed."

Page 438 (on manic illness):

"Until there is more specific knowledge as to methods of decelerating diencephalic activity, which is at the basis of the manic illness, three general procedures are of value. . . ."

The idea identifying the diencephalon as the point of origin in manic depressive illness is found throughout the book. On page 494 Kraines writes:

"Cortical function must depend on subcortical stimulation. . . . As the result, the cortex will respond to stimuli that are different-from-usual, and give rise to a psychic response that is different-from usual. It is this distorted psychic response which is often mistaken as a cause, whereas it is only a symptom.

According to Penfield[10] and Magoun:[11]

"Consciousness continues to exist . . . as long as the centrencephalon remains intact. This central core (the centrencephalon) which includes the diencephalon and the reticular system, appears to act as an alerting mechanism energizing the cortex to action. . . . In the manic depressive Illness the disturbance of consciousness results from this centrencephalic change rather than from any primary alteration in the cerebral cortex."

A similar interpretation of manic depressive illness is advanced by Leo Alexander.[12] This author feels that a primary or 'alerting anxiety' is generated in diencephalic areas which stimulates the cortex, creating overt behavioral manifestations or may overstimulate the cortex to the point where a paradoxic Pavlovian response occurs, and this manifests itself in the overt symptoms of depression. In discussing psychotherapeutic agents Alexander[7] states:

"Their effect is achieved by inhibition of primary subcortical epinephrine-precipitable anxiety, probably by exerting a selective inhibitory effect upon the posterior hypothalamus."

Finally, in this connection, the constant inescapable anatomic interrelationship between primitive brain areas and the neocortex must be acknowledged. James W. Papez[13] writes:

"The visceral brain or rhinencephalon consists of several closely-connected mechanisms — olfactory, alerting, visceral, emotional and autonomic. These parts are closely integrated to coordinate sensory events with bodily and visceral needs. They are biologically grounded and are closely bound in action to regulate flight and emotion-provoking situations in the body and in the environment."

W. Ross Adey[14] reasons:

"It is reasonable to suggest that certain cortical areas exercise a prior influence on the great stream of neural activity ascending in the reticular formation, by reason of reciprocal interconnections between reticular and cortical areas, activity so initiated may be of a re-entrant or reverberant kind, maintained over considerable periods in the . . . required alternating process. The results outlined here suggest that the cortex of the limbic ring, and particularly the zones of amygdaloid and entorhinal cortex, may exercise such an influence."

Pharmacological Aspects:

It is becoming increasingly clear that different biochemical factors, sometimes agonistic and antagonistic chemicals, are responsible for the different symptoms regardless of whether these symptoms make their appearance in mental illnesses classified un-

der one or another diagnostic category. Brodie[15] has summarized the results of recent biochemical research and the following quotations are taken from this article:

"It had been evident for some time that the two divisions of the peripheral autonomic system, the sympathetic and the parasympathetic, have representation in the central nervous system . . . like the peripheral autonomic nervous system, the subcortical system consisted of two separate and antagonistic divisions—ergotropic and trophotropic."

This is based on a concept advanced by W. R. Hess.[16]

"The overall effects of *ergotropic* stimulation are arousal, increased sympathetic activity and enhanced skeletal muscle tone and activity, and an activated psychic state. In contrast, the *trophotropic* division integrates parasympathetic with somato-motor activities to produce behavior patterns that are recuperative and protective in nature. Both neuronal divisions may be considered not as normally quiescent, but rather in a balanced state of activation or tone."

Brodie further advances this theory:

"Serotonin and norephrine may qualify as *neurohormones* for the two divisions, since the amines as well as the enzymes involved in their formation are localized chiefly in those areas of the brain where Hess found evidence for the trophotropic and ergotropic divisions, i.e., the brain stem, especially the hypothalamus."

Special consideration is given to amine-oxidase inhibitors and the observations published by Spector, S., Prokop, D., Shore, P. A., and Brodie B.[16] and Olds, J., and Olds, J., and Olds, M. E.,[17] indicate that:

"Marsilid given to laboratory animals in small daily doses progressively elevates the brain levels of both serotonin and epinephrine until they reach two to three times their normal values in a few days. At this time there appear signs of sympathetic stimulation, including . . . psychomotor excitation. There is evidence that the increase in brain norepinephrine may be responsible for the stimulatory effects of the drug."

However, with reference to the value of psychotherapeutic drugs, Brodie states:

"The question arises whether psychotherapeutic drugs cure mental illness. Reserpine and chlorpromazine do not alter the basic defects in mental disorders but provide symptomatic treatment. . . . In mental diseases associated with psychomotor hyperactivity and exaggerated emotional responses, the tranquilizers swing the pendulum in the direction of trophotropic predominance. Mood-elevating agents such as amphetamine and monoamine oxidase-inhibitors influence the symptoms of patients with depression by swinging the pendulum in the direction of ergotropic predominance."

The quotations from Brodie's paper on psychotropic drugs are based on his own investigations in the Institute of National Health, Bethesda, Md., as well as on investigations of his co-workers, and furthermore on investigations published by Olds,[17] Himwich[18] and others.

The existence of centrally acting neurohormones which stimulate adrenergic (norepinephrine) or cholinergic (acetyl-choline) predominance is further augmented by Domino, Edward F.[19] by the inclusion of serotonin. Domino states with reference to serotonin:

"Because of its presence in the central nervous system . . . its release by Reserpine and its blockage by LSD 25 has provided much data," and so on. "The intravenous administration of serotonin produces an EEG arousal. Since serotonin is a potent stimulant of chemo receptors, some of its central actions might be explained on this basis. . . ."

At our present stage of knowledge regarding drug therapy, it might be well to remember that it is important to select the drug to fit the symptoms rather than to fit the diagnostic category. This is so because in our present classification one category may include either retardation or agitation. The use of tranquilizers has been suggested in both hyperactive and hypoactive patients, because anxiety is supposed to be at the root of either symptomatology, and this may be true in many cases. Following this line of thinking all depressive (retarded) symptoms would have to be due to excessive stimulation of the cortex by an overactive diencephalon, and a Pavlovian paradoxic response of the cortex (L. Alexander). However, it seems reasonable to assume that some retarded depressions may be due to a true lack of alerting stimuli from the primitive brain, and these are probably the cases which do not respond favorably to the administration of tranquilizers, in particular reserpine. The observation that tranquilizers aggravate or even cause depressions is probably based on this fact.

If we were to review our concept of depression and accept the theory that true de-

pressions must be associated with a lowering of vitality and retardation of psychomotor functions, and if we were to place the opposite symptoms such as agitation, nervousness and increased psychomotor activity in a different diagnostic category, rather than labeling them as a depression of a different type, we might then arrive at a logical understanding of neurohormonal factors which are responsible for the appearance of the depressive symptoms.

Evaluation of Treatment Results

Manic depressive illness is a disease which has a spontaneous recovery rate, and all therapy of depression should be evaluated in comparison with figures of spontaneous recovery. Such figures have been published by Alexander.[12]

It was also indicated earlier that tabulation of treatment results with chemical or physical means is of limited value, as long as we are not able to classify the disease to be treated on an etiological basis. This applies to drug therapy as well as to electrotherapy. The limited value of such tabulation consists of the possibility of sharing empirical knowledge with others. It is only with this understanding that the following treatment results are published at this time.

Marsilid

Iproniazid (Marsilid—Roche) has proved to be of value to some patients with various symptomatologies which had previously resisted therapy with other means. A total of 73 patients were treated with Marsilid and the treatment results tabulated. Of these 11 were diagnosed depressive states, 18 catatonic, and 12 as chronic brain syndrome. Since Marsilid is said to have analeptic energizing properties it was used on patients who showed a slowing down of their activity and interest, no matter whether the picture was that of depression, neurotic or psychotic, or whether the patients showed signs of schizophrenic withdrawal, regression or stuporous catatonia.

It is comparatively easy to get an overall impression of treatment results and this impression is that favorable results have been achieved with Marsilid in a number of cases previously resistive to other therapies. However, an attempt is made to arrive at more objective figures by grouping patients in diagnostic categories according to the A.P.A. manual. The evaluation of improvement of a patient is indicated by a number of plus marks, 1 to 4 (Table 1).

TABLE 1

Tabulation of Clinical Results With the Use of Marsilid

Diagnosis	Total No. Patients	Excellent ++++	Marked +++	Moderate ++	Little or Temporary +	No benefit	Discontinued (side effects)
Depressive States	11	3	5	1	2	0	
Catatonic Schiz.	18	4	2	6	1	2	3
Chronic Schiz. other than Cat.	32	4	1	8	10	9	7
Total	73	11	8	21	16	12	12

All patients in this study had shown no response to previous treatment including electrotherapy. Some had been hospitalized for many years.

Marsilid has also proved to be of value in stuporous catatonic schizophrenics in combination with electroshock therapy, when ECT alone or in combination with phenothiazines had produced no lasting effects. Four out of 18 previously resistive cases of catatonia have recovered with concomitant ECT and Marsilid therapy.[21] The property of Marsilid to increase appetite has proven valuable in all patients who refused to eat.

Side-effects listed in the order of frequency were ankle edema, increased agitation, hypotension (when used in combination with reserpine) and occasional seizures. An early sign of toxicity is hyperreflexia, and this can be used as a warning symptom to obviate more serious side-effects by reducing the dosage. According to a recent report by Killiam[22] seizures can be avoided by adequate administration of Pyridoxine (Vitamin B_6).

Deprol

Deprol (Wallace Laboratories) is a combination of meprobamate and benactyzine. Its use in the treatment of depressions has been recommended by Leo Alexander[12] on the basis that benactyzine "facilitates the orienting response and the formation of new conditioned reflexes, thus counteracting the inhibitory state of high cortical activity," and meprobamate "has no recognizable or

significant or anti-depressant effect, but appears capable of reducing excitability without producing inhibitory states."

Of 31 patients treated with Deprol, 13 were agitated depressions, including involutional types, six were psychotic depressive reactions, four were diagnosed as manic depressive reaction, 7 were classified as neurotic depressions, and one patient with a chronic brain syndrome and depression also received the medication. The dosage varied from three to 6 tablets per day. As is indicated in the accompanying chart, very few patients showed improvement to a degree where the evaluating personnel felt that improvement was excellent. Evaluation was based on observation of various symptoms such as crying, disturbance of appetite, disturbance of sleep, agitation and restlessness, sadness, etc.

TABLE 2

Tabulation of Clinical Results With the Use of Deprol

Diagnosis	Total No. Patients	Excellent +++	Marked ++	Moderate ++	Little or Temporary +	No benefit -	Needed Electrotherapy
Agitated Depress.	13	2	0	3	2	3	10
Psychotic Depr. reaction	6	1	2	0	2	3	3
Manic-Depressive reaction	4	0	0	1	2	1	2
Neurotic Depress. reaction	7	1	2	1	2	1	2
CBS with Depress.	1	0	0	0	0	1	0
Total	31	4	4	5	8	7	17

Side effects: Increased agitation, dizziness, nausea.
Dosage: 3 to 6 tablets p.d.

The results observed can be seen in the accompanying table (Table 2). It should be pointed out, however, that in 17 of the total of 31 patients it was necessary to institute electrotherapy, and that only four of the total responded to a degree where all symptoms disappeared. The side-effects observed were increased agitation, dizziness and nausea, and it was necessary to discontinue Deprol therapy in several patients.

In comparing the results with Marsilid and Deprol, it would appear that Marsilid was more effective in the treatment of depressions than Deprol, particularly for the reason that the patients treated with Marsilid were individuals who were previously treated without lasting results by other therapies, while the group of patients on Deprol were treated merely on the basis of their depressive symptoms without attempting other therapies first.

Electrotherapy:

Recovery rate in 68 depressed patients treated with electrotherapy was 88.2% during the first six months. This figure is higher than previously published results,[12] and this fact is attributed to the selective use of diencephalic stimulation as described elsewhere[23] and discussed in the following paragraph. Detailed results are given in Table 3.

TABLE 3

Tabulation of Clinical Results With the Use of Electrotherapy
(Cortical and/or Diencephalic)

Diagnosis	Total No. of Patients	Recovered
Psychotic Depr. React.	6	6
Manic Depr. Depr.	7	6
Manic Depr. Manic	14	14
Manic Depr. Mixed	2	2
Involutional Psych. R.	21	16
Neurotic Depressive	10	10
Schizo-affective	8	7
	68	60
		88.2%

True knowledge of the mechanisms of electrotherapy in psychiatry will be available only after the direct effect of electric currents on the various parts of the brain is studied experimentally, and such experiments are now under way. Of all the theories presently available the one recently advanced by Alexander[12] seems to fit our experience best. This theory is summarized in two paragraphs (page 44): "In sum the total effect of nonconvulsive electric treatment is one of stimulation of activity of the nervous system . . ." while (page 46) ". . . the effect of convulsive electric treatment is obviously one of reduction of excitability of the nervous system."

At this point I would like to advance a somewhat more complex theory concerning the action of electrotherapy which is based on experience with conventional ECT, which we shall call *cortical* therapy, as well as on

experience gathered with *diencephalic* therapy, which is outlined elsewhere[23] (Table 4).

TABLE 4

Hypothesis on the Effects of Cortical and Diencephalic Electrotherapy

PREMISE: Low currents (non-convulsive) excite.
High currents (convulsive) inhibit.

CORTICAL (C):

(a) C—Non-convulsive
low in cortex
low in diencephalon
(primary and secondary excitement of cortex and diencephalon with resulting increase of anxiety)

(b) C—Convulsive
high in cortex
low in diencephalon
(primary calming of cortex which may abandon Pavlovian paradoxical response and begin to function again. Secondary excitement of diencephalon adding to cortical activity. This works in true depressive states.)

DIENCEPHALIC (D):

(a) D—Non-convulsive
high in diencephalon (see text)
negligible in cortex
(primary calming of diencephalon—secondary improvement of cortical function. This works in anxiety and mania.)

(b) D—Convulsive
high in diencephalon
high in cortex
(primary calming of diencephalon, secondary calming of cortex. This reduces anxiety as well as hostility and works in paranoid conditions.)

We take for granted that low currents (non-convulsive) increase, and higher currents (convulsive) reduce the excitability of the nervous system. However, while the density of the electrical field varies and depends on the intensity of the applied currents, it also depends on the locale of their application (cortical or diencephalic). Thus, *cortical* therapy with *non-convulsive* currents, increases the excitability of the entire brain, while *cortical* therapy with *convulsive* currents decreases the excitability of the cortex, while increasing the excitability of the diencephalon. We thus see anxiety coming to the fore as depression improves.

In diencephalic therapy we invariably stimulate the diencephalon with comparatively high currents (thus decreasing its excitability). This is true because of the closeness of the small electrode to the diencephalon and the vastly different resistance of the interposed structures, namely, the low resistive pharyngeal mucus membrane as compared with the highly resistive scalp. In taking these factors into consideration and realizing that in all diencephalic stimulation a calming effect in the diencephalon is thus accomplished, we understand why diencephalic therapy acts favorably in all states of hyper-irritability of the diencephalon such as anxiety neuroses and manic state. We also understand why diencephalic therapy does not primarily or immediately improve those conditions in which manifestations are based on dysfunction of the cortex per se, or where damage to the cortex has already resulted, such as in true retarded depressions or catatonia. Nor does diencephalic therapy *directly* accomplish a disappearance of delusions or hallucinations, if such disorders have resulted from a long-existing abnormality in the diencephalon, and such diencephalic abnormality has led to the establishment of abnormal processes in the cortex.

However, if we assume that a diencephalic disorder is at the basis of most psychoses then diencephalic therapy has a chance also in the treatment of long-existing illness of the cortex, if it is given sufficient time for recovery. Our experience in paranoid conditions definitely corroborates this theory. In manic states (which usually have not existed for long periods of time because mania is self-healing in most cases), the calming of the over-active diencephalon by electric stimulation produces recovery very quickly. Detailed treatment results corroborating these statements have been published.[23]

It is interesting and instructive to know that those mental disorders which do not respond to electroshock show the best prospect of improvement with diencephalic stimulation. These conditions are anxiety states, mania and paranoid conditions. The treatment techniques (D or C) should be selected according to the predominant symptomatology such as agitation or retardation, rather than on the basis of diagnostic entities.

Conclusions

A review of the literature concerning manic depressive illness reveals that the illness basically may be one of a somatic, bio-

chemical or endocrine origin, while it is also quite evident that psychological as well as hereditary and constitutional factors may be contributing and always exert a modifying influence on the overt manifestations. These manifestations vary to a degree where many different names and classifications have been suggested to identify illnesses which quite possibly might be of one origin.

Anatomic and physiologic studies carried out most recently indicate that there may be one area of origin for various disturbances of the brain. These recent studies indicate that the original disturbance may attack the primitive brain, particularly the diencephalon, and subsequently lead to disturbance in the neocortex which we then see in the patient's behavior, mental content and emotional reactions. If this theory is true, then whatever results we accomplish in the treatment of the disorder must corroborate the theory, and indeed therapeutic results do confirm this concept. This is true about drug therapy, because there exists no disagreement on the fact that all psychotherapeutic drugs in use today are modifying the diencephalic functions in one way or another.

It is also true that electrotherapy is an accepted treatment of depression all over the world, and electricity is something which cannot be labeled as psychologic.

It has been pointed out in this paper and others that electrotherapy can be improved in its results by the use of diencephalic stimulation, which further elucidates the fact that the basis of the illness may lie in the diencephalon.

Like in other diseases in which body chemistry is disturbed, the balance of forces may be shifted in the direction of excitation or inhibition and accordingly we see the manifestations of agitation or retardation appear. Agitation may express itself in manic or paranoid conditions, while retardation is a depressive symptom. It is suggested that the term 'depression' be reserved for this type of disorder. It appears that somatic treatment of mental disorder should be one which stimulates or inhibits nervous tissue in accordance with the presenting symptoms. It seems unreasonable, for instance, to treat agitation as well as retardation with the same type of electric stimulation or the same type of drugs. The results obtained with drugs and selective use of electric stimulation (cortical or diencephalic) corroborate the theory advanced by various authors recently that the disorder originates in primitive areas of the brain, i.e., the diencephalon or the reticular system. This is also the area where psychotherapeutic drugs are useful.

Results with selective electrotherapy seem to corroborate Alexander's theory that strong electric currents blunt the reaction (raise the threshold of excitability) while weak currents increase excitability of the nervous tissue. Based on this premise a theory explaining the effectiveness of psychiatric electrotherapy is offered.

Marsilid has been found to be an effective drug in the treatment of depressive states and catatonic schizophrenia, and has made recovery possible when electrotherapy or other drugs, or both, have failed.

Deprol has been found useful in some cases of depression, but has not obviated the need for electrotherapy in at least half of the cases in which Deprol was tried first.

Electrotherapy still seems to be the most effective tool in the treatment of affective disorders, particularly when techniques are varied between cortical and diencephalic stimulation, in accordance with the presenting symptoms.

Summary

1. A review of the psychiatric literature reveals that there is discrepancy in the definitions of mental depression, inasmuch as these definitions are admittedly based on manifestations and not on etiology, and yet sometimes quite unrelated symptoms are included in one diagnostic entity, while symptoms similar to one another are grouped in different categories. The inclusion of various unrelated symptoms in one classification would not matter if this classification were based on etiology rather than symptoms. However, as long as we are using only descriptive criteria the inclusion of opposing symptoms under one category is confusing.

2. In an attempt to arrive at a more valid definition, the etiology of depression is reviewed and the information presented in favor of analytical, somatic and chemical aspects. In the light of recent findings in the

field of neurophysiology and pharmacology, it appears that the disease most likely has its origin at least partly in a disturbance of the function of diencephalic brain areas. A reciprocal relationship between this area and the neocortex is generally acknowledged but psychotherapy is of limited value as long as a disturbance of diencephalic function exists. The aim of therapy therefore should be to treat this disorder as well.

3. Results with drugs and selective electrotherapy indicate that the disturbance of diencephalic function may be one of excessive or insufficient activity and responsiveness, and that this may in some instances alternate.

4. It is suggested to limit the use of the term "depression" to those conditions which are characterized by inhibited cortical activity (retardation). Agitation and mania, while attributable to a disturbance in the same general brain area, are probably of a different nature and accordingly respond to a different therapeutic approach.

5. Tabulation of treatment results with drugs and electrotherapy is valuable only as a means of making available empirical knowledge to others, but in itself does not justify conclusions as to the value of a specific therapy when this therapy is applied to a group of possibly unrelated diseases, even though labeled by the same name.

6. It is possible today to stimulate or inhibit nervous tissue with drugs or electricity selectively. Within the limitations outlined under Point 5 results of treatment of depressions with Marsilid, Deprol and electrotherapy are reported.

7. A theory explaining the effects of electricity upon the brain is offered which takes into consideration not only the intensity of currents used, but also the localization of the greatest density of the electrical field.

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Psychodynamic Alterations Concomitant with Intensive Meprobamate Administration

H. AZIMA, M.D., JADWIGA SANGOWICZ, M.D., JOAN SPINDLER, B.A., and FERN J. AZIMA, M.A.

Since the introduction of newer pharmacotherapies in psychiatry the main body of published reports has concerned itself solely with the gross behavioral alteration, subsequent to drug administration. As we have pointed out elsewhere[1-4] after certain such studies it became desirable and necessary to go beyond behavioral observations and try to determine the effects of pharmacological substances on psychodynamic states and mental structure. Only by this kind of investigation may we hope to learn enough about the actions of drugs on the mind to enable us to alter directly the psychotherapeutic or psychoanalytic field in the future. The lack of such studies is particularly evident in connection with meprobamate. Since Berger's introduction of this substance[5,6] a considerable number of papers have been published, all pertaining to its gross clinical effects. The purpose of the present paper is to report on the result of a study where the aim was the detection of change in psychodynamic states concomitant with large doses of meprobamate.

Methodology

The method of the study was similar to the one devised by the senior author and reported in connection with the psychodynamic investigation of the effect of reserpine.[4] Due to the importance of methodology, we shall reiterate its relevant points here under four headings: Patients; Drug Administration; Collection of Observations; and Method and Sectors of Observation.

1. Patients.

Fifteen hospitalized patients were selected for this study. An attempt was made to choose only "typical" cases, in order to facilitate the psychodynamic inferences and avoid the difficulties encountered in complex clinical pictures. Diagnostically they consisted of five schizophrenics (one simple and four paranoids); two borderline states; one depression and one hypomanic state; two obsessive compulsives and four anxiety neuroses. There were 11 females and four males with an average age of 35 years (the oldest being 44 and the youngest 17). All patients could be classified as "acute," i.e. the duration of overt symptomatology was not more than one year and they all were hospitalized for the first time. The reason for the selection of "acute" states was the assumption that in so-called chronic state the personality structure is deeply engraved by pathological processes, and ego defenses are of long standing, more rigid and less apt to change, while recently occurring psychopathology indicates more flexibility and readiness for regression-progression movements and hence is more informative from the point of view of change detection. In addition the necessity for patients to be hospitalized indicates a considerable intensity of their disequilibrium, which, theoretically at least, made it easier for the detection of change than in those patients with less intense disequilibrium treatable on an outpatient basis. Hence by taking "acute," "typical" and "hospitalizable" patients, it was thought that the production and detection of change would become more feasible.

2. Drug Administration.

A uni-blind method of drug administration was adopted consisting of three periods: no-drug—meprobamate period—no-drug period. The first period of no-drug observation lasted for two weeks, the drug period for four weeks and the second no-drug period was divided into hospitalization phase of two weeks and out-of-hospital follow-up phase of four to nine months. Meprobamate dosage was arranged in such a way to reach 10 to 12 gm per day by the 10th day. The

From McGill University and Allan Memorial Institute, Montreal, Canada.

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beginning dose consisted of 1½ gm daily. In three instances the drug had to be decreased to 6 gm because of uncomfortable motor incoordination and other side effects.

The reasons for using such large doses of meprobamate were as follows: (1) the severity and acuteness of the patients status, indicating the possible ineffectiveness of the usual low and medium dosage of meprobamate; (2) the idea of comparing prolonged sleep with phenothiazine-barbiturates with meprobamate sleep; (3) the absence of published reports on intensive meprobamate administration of the magnitude described in this paper; (4) a naive theoretical assumption—which in some instances is tenable—that the more we use of a drug, the more manifest the changes may turn out to be.

Meprobamate was stopped abruptly at the end of the fourth week. The reason for this sudden cessation of medication was (1) to study the effects of sudden withdrawal and (2) to compare the results with those of barbiturates. In previous studies with sleep treatment using barbiturates[7] the medication had been stopped suddenly at the end of the 25th-30th day of sleep and it was thought that comparison of the two post-medication states would give information about the similarity and differences of the two drugs.

3. Collection of Observations.

The observations consisted of two sets of data: clinical and psychological tests. Clinically the patients were interviewed two to three times a week in all periods during which they were hospitalized, and from four times to once a month subsequently. The interview sessions lasted from 30 to 50 minutes, during which a sample of the patient's free association was recorded and a phenomenological appraisal of the patient's state was made, to serve as a reference from which to infer psychodynamic changes.

The data were analyzed separately by two observers, one who did the interviewing and the other who acted as a control-observer, going over the data independently from the first observer.

Twelve patients were tested with EEG before and at the peak of meprobamate administration. The results of these tests will appear elsewhere[8] and will not be discussed here.

Psychological Testing

A battery of psychological tests consisting of Rorschach, Figure Drawings, Bender Gestalts and an abbreviated Wechsler Bellevue scale (subtests of Digit Span, Arithmetic, Block Design and Digit Symbol) was administered before and just prior to the cessation of meprobamate. The plan was the assessment of change in the tests at the point of maximal drug action. Due to admitting problems some of the Wechsler Bellevue's subtests could not be carried out in three patients. Figure Drawings were, in addition, obtained once a week throughout the experimental period.

Two psychologists were involved in the evaluation of test data, the first functioning as the tester and the second as the control psychologist. Both psychologists were unaware of the nature of the drug and the design of the experiment and both analyzed the data independently. The control psychologist (F.J.A.) evaluated and statistically analyzed the data obtained by the first psychologist.

The Rorschach and Wechsler Bellevue were analyzed for general trends and for statistical significance of test items. Tests computing probabilities from the standard error of the difference for paired observations were utilized.[9]

4. Method and Sectors of Observation.

It should be reiterated here that the aim of this study was not therapeutic, but the detection of change in psychodynamic state. Because of this, the collection of observations was emphasized in a certain direction involving the following points:

(1) Three areas where the changes were thought: Ego, drives and object-relations (internal and external).

(2) Three sectors of observations from which the inferences about the above three areas were made:

(a) Organization of overt behavior, particularly in regard to quality (the mode of interpersonal relations, i.e. loving-hating) and to quantity (the intensity of interper-

sonal relations) of external object relations.

(b) Organization of mood, consisting of four states: anxiety, depression, elation and indifference. This sector of observation was particularly taken note of because it was felt that the alterations of mood—theoretically at least—were indicative of a change in the economic balance of the mind (in the psychoanalytic sense) and in addition it was recordable objectively (from overt behavior and thought content) and reportable subjectively.

(c) Organization of thought: consisting of its formal aspect (rate, logical consistency, etc.) and its content.

(3) The technique of interviewing: In order to minimize the effect of transference and counter-transference phenomena and to reduce as much as possible their therapeutic element, three points were emphasized in the technique of interviewing:

(a) Encouragement of free association.

(b) Withholding of interpretation and explanation in order to allow the spontaneous upfolding of psychic processes.

(c) Introducing of two separate observers (the interviewer and the control-observer) and a psychologist, independently analyzing the data and reaching conclusions.

(4) Two criteria of assessment of change:

(a) Taking the patient as his own control, and by closely comparing the usual personality characteristics with what happens during pharmacotherapy, to reach conclusions about drug-induced or spontaneous changes. We submit that in studies involving psychodynamic states comparisons of two patients with similar symptomatology is less informative than the study of one patient, whose inner world is well known to the observer during different times of study, i.e. drug and no-drug periods.

(b) Taking two concepts of "incomprehensibility" and "emergence" as the most reliable characteristic of psychological events not related to psychotherapeutic processes, including transference phenomena. We submit that an event is "emergent" when it is "incomprehensible" to the observer, who is quite familiar with the patient's inner world, in regard to what he knows about the reactivity and the responsivity of the patient and the evolution of the latter's psychic processes. And if—and only if—this "emergent" event is concomitant with the intake of a drug, a probability of relation between the event and the drug may be assumed. As we have pointed out previously,[4] the "comprehensibility" is a subjective judgment, depending upon the intensity of the observer's knowledge of the patient's inner world and it is a relative appraisal. However, we feel that in psychodynamc iresearch the opinion of the observer *is* the main criterion of relevance of a given event, and we have to rely on this opinion in our inferences. Only the improvement of the therapist and the repetition of the same experiments by similar observers can settle the issue.

Results

We shall present the results under three headings: Behavioral, psychodynamic, psychological test changes—the main objective being the change in psychodynamic states. The description of behavioral changes and therapeutic results will be quite brief. It should be also noted that the appraisal of the two observers of clinical data agreed quite closely with each other and there was no instance of a sharp discrepancy.

I. Behavioral Changes.

We shall consider behavioral changes during and immediately after meprobamate administration.

During the drug period five patients complained of dizziness, two of unsteady gait, two patients manifested psychomotor retardation and five drowsiness. It was noted that contrary to our expectations the degree of drowsiness was mild and no patient went into a prolonged sleep. This is in contrast to the barbiturate effect, which in large doses is usually hypnotic. Two explanations may be given for this phenomenon: (1) The gradual increase in mephobamate dosage, which reached its maximum within 10 days, hence possibility of habituation; and (2) dynamic changes different from those produced by barbiturates and preventing a deep sleep (see discussion).

Immediately after the cessation of meprobamate, nine patients developed nausea and

vomiting, two a confusional state and two epileptic seizures. The latter two patients had only one seizure each, there being no evidence of epilepsy in their history. These complications were seen as a part of withdrawal symptoms. They lasted from 2 to 7 days and disappeared spontaneously.

II. Psychodynamic Changes.

We shall describe these changes in each diagnostic category according to the four areas mentioned in methodology, i.e. organization of the ego, of drives, of object relations and of mood. It should be noted that the changes described are those which appeared "emergent" to the observer, that their appraisal was relative and the division of different areas arbitrary.

1. Schizophrenic States.

There were five patients in this category, four paranoid and one hebephrenic in their clinical structure. The following changes were observed:

(a) *Organization of the Ego:* This was considered from the point of view of defensive and executant functions of the ego. In general there was a change in schizophrenic defenses of withdrawal, splitting and projection. Three patients showed a decrease in projection mechanisms, in two this was followed by an increase in introjection (inferred from the shift of persecutory anxiety to depressive anxiety), and in one by denial. In two patients splitting mechanism disappeared (inferred from the disappearance of confusion and a state of being in bits) and was followed by denial and secondary narcissism (self aggrandising feelings). In another patient the withdrawal decreased and was followed by denial.

The executant function, judged by total reality responsivity and reorganization of object relations, improved in four cases during the treatment and in one case after treatment. One patient relapsed after two weeks; the other four patients have continued their improvement up to the time of writing, i.e. six months after the cessation of meprobamate. In three patients the improvement seems to be due to the persistence of the denial mechanism and in the other to the partial splitting (encapsulation of the delusional system and splitting of it from other parts of the psyche).

(b) *Organization of Drives:* In general there was a moderate release of both aggressive and libidinal drives, the former predominating. Only in one case was the release of aggression violent, in form of agitation, running out and anger. In one patient a decrease in oral activity occurred in form of decrease in appetite and the desire to smoke.

(c) *Organization of Object-Relations.* Changes in the ego organization and drives led to certain reorganization of object relations. Responsivity and ability to contact with the external world increased in four patients. In one of these the ambivalence became more marked in object relations. This was inferred from the patient's concomitant libidinal attachment to the observer and increase in guilt feelings. Another patient experienced a lessening of feelings of being destroyed and more coherence and intactness in his existence. In one patient there was a relative disturbance of existing object relation due to decrease in systematized paranoid projection and flooding of the field of consciousness by persecutory and depressive anxieties.

(d) *Organization of Mood:* In general there was a mood change towards depression-elation states. Three patients experienced elation, one in form of hypomania and two in form of expansivity and megalomania. Two patients developed depressive states, in one of whom this was associated with marked anxiety of both depressive and persecutory type.

In summary then, there appeared a change in schizophrenic defences, a certain reorganization of object relations associated with a depression-elation mood swing. The picture was that of a progression movement, which continued after the cessation of meprobamate.

2. Borderline States.

There were two patients in this category. Ono patient showed a regression towards a schizophrenic state under meprobamate. A break in the patient's character defenses was observed concomitant with a release of orality (demanding, forcefully seeking reassur-

ance, etc.), agitation and aggression. He became, at times, so unmanageable in the ward that he had to be sedated with I.V. Sodium Amytal. It was noted that his agitation and aggression increased with the increase in the dosage of the drug. Associated with these he showed a marked depression-elation mood swing, the mood changing from one state to another within an hour or so.

The second patient showed a mixed picture of regression and progression. She showed a release of aggressive drives at the beginning, which later was partly introverted and produced a depressive state. However, she became more responsive, more realistic, less depleted and more vigorous in her activities.

Both patients returned to their pre-meprobamate state after the cessation of the drug.

In summary then the clinical picture during the drug period was a mixed one in these two borderline states.

3. Manic-depressive States.

There were two patients in this category, one depressed and the other hypomanic. The depressed patient showed no appreciable change during meprobamate administration, while the hypomanic patient became manic and so unmanageable that he required barbiturate sedation in several instances. He returned to his hypomanic state after the cessation of the drug. It was difficult to explain the development of this manic state. The argument that mania was a more vigorous denial of an underlying depression, which was going to be experienced, did not seem valid because chlorpromazine successfully controlled his hypomania afterwards.

4. Obsessive Compulsive States.

There were two patients in this category suffering from marked and long standing obsessive-compulsive neurosis which had remained refractory to all forms of therapy. Their response to intensive meprobamate administration was similar. This consisted of a break in and a disappearance of obsessional defenses and behavior, the release of sexual and aggressive wishes and phantasies, associated with marked anxiety and depressive features. One patient developed intense panic attacks of being assaulted by men. In both patients a change in object-relations occurred in form of anxious libidinal preoccupation with external objects. Their associations contained with increasing frequency, sexual problems, which, at the beginning, were concomitant with marked anxiety and guilt feelings, which disappeared after the cessation of the drug and left a better organized libidinal and aggressive object-relation.

Post meprobamate clinical results were marked improvement in both patients. One patient relapsed after three weeks, but the other has remained symptom free up to the present, i.e. about eight months after the cessation of meprobamate.

5. Neurotic Anxiety States.

There were four patients in this category. The following changes were noted:

(a) *Organization of the Ego:* All patients manifested an abandonment of repression mechanism of defense and showed an increasing use of the mechanism of introjection (inferred from the appearance of guilt feelings, self-condemnation, withdrawal, etc.). The impression was that a regression did occur to the depressive mode of defense.

(b) *Organization of Drives:* Concomitant with the lifting of repression a release or disinhibition of drives seemed to occur, particularly in form of aggressiveness clearly discernible in three patients, verbally and nonverbally. In one of these a sado-masochistic mode of behavior emerged clinically. In three others the emergence of oral conflicts could be inferred from the loss of appetite and the disappearance of the need to smoke.

(c) *Organization of Object Relations:* There was a gradual shift to an excessive preoccupation with the self and inner world (internal object relations) in all patients, in two of which the withdrawal was quite marked. In two other patients there was outburst of aggressiveness which gave the appearance of more responsivity to the external objects. However, this was seen as an aggressive reaching out related to the disinhibition of drives.

(d) *Organization of Mood:* All four patients developed a clear clinical picture of depression, characterized by guilt feelings,

uncontrollable crying, etc. This depressive state became apparent during the second week of meprobamate administration and disappeared after its cessation.

The general clinical response after the drug period was marked improvement in all patients which has been maintained up to the present time, i.e. about nine months after the cessation of meprobamate.

In summary then, there appeared a break in the repression mechanisms and a regression to depressive states in all patients.

III. Psychological Test Results

We shall consider these results from the point of view of statistical analysis of test items and the common denominator of change rather than detail reports of change in each patient or each category of illness. These will be reported elsewhere.

The Wechsler Bellevue and Rorschach were analyzed for statistical trends. Reported in Table I are the results of this analysis, which revealed statistical significance or trends within the group.

Wechsler Bellevue Subtests

It can be seen from the table that the four repeated Wechsler subtests all showed impairment at the point of discontinuance of the drug. At the significant level (p—.01) the Digit Span and Digit Symbol subtests showed impairment in the areas of concentration and recent recall and learning. On the Block Design and Arithmetic subtests 8 and 7 out of the 12 patients retested diminished respectively. This diminution in intellectual functions was felt to be a resultant of the combination of toxic effects plus emergence of psychological imbalances that served to impair the patient in the areas of concentration, learning, visual motor organization and arithmetical reasoning. We consider these alterations to be indicative of an ego disorganization and regression.

Rorschach

An examination of all the usual Rorschach indices and quantifications revealed that the number of responses and the Sum Color diminished in the retesting period, which was at the borderline statistical level (p—.1). Other important trends appear in the number of responses to the last three all-colored cards, where eight of the 15 patients showed less responsivity, while seven of the group showed less use of Animal %. The overall findings indicated that for most of the group there was a decline in productive or energy output, plus less spontaneity and responsiveness to the environment. These findings, on the whole, suggested the emergence of depressive features and withdrawal reactions.

Discussion and Conclusions

The above data indicate that concomitant with intensive meprobamate administration the following events seem to emerge in the psychodynamic field: (1) a change in the ego organization which manifested itself as progression in schizophrenics and regression in neurotic and borderline states; depressive state remaining unaffected. (2) The emer-

TABLE I

TRENDS IN WECHSLER BELLEVUE AND RORSCHACH INDICES CONCOMITANT WITH MEPROBAMATE ADMINISTRATION

Wechsler	No. of Pts.	Direction of Change +	—	0	Mean Pretest	Mean Retest	S.E. of diff.	p
Digit Span	12	2	8	2	6.42	4.72	0.42	<.01*
Digit Symbol	11	1	10		7.45	4.27	0.65	<.01*
Block Designs	12	4	8		7.33	6.08	0.97	<.3
Arithmetic	12	4	7	1	7.83	6.66	0.96	<.3
RORSCHACH								
Number of Responses	15	1	11	3	23.27	19.53	1.46	<.1†
Sum C	15	4	6	5	2.30	1.73	0.33	<.1†
R/8, 9, 10	15	5	8	2	32.33	30.53	3.25	>.6
Animals %	15	3	7	5	4.85	4.59	2.29	>.9

† Very significant.
* Borderline significance.

gence of drives, particularly aggression. (3) The appearance of depression-elation mood swings, the depression being the common denominator of change. This latter observation was corroborated in projective tests at the borderline level of statistical significance. (4) Sustained clinical recovery in the majority of schizophrenic and neurotic patients after the cessation of meprobamate.

The theoretical problem is how to relate these observations to one another, and how to relate them to the action of meprobamate. Taking the observations in their most essential form, it can be seen that the basic change was that of mood (depression in particular) in the background of a regression-progression movement, the former mainly in neurotics and the latter mainly in schizophrenics. The paucity of data does not permit any definitive theoretical statements. However, certain tentative conclusions may be outlined aiming at raising issues rather than settling them. In general the problem can be considered from two angles: organic and dynamic.

1. Organic Hypothesis.

Due to the very large doses of meprobamate it can be said that all the observed changes were due to the "toxic" effect of the drug. Undoubtedly this is a relevant point; however, by terming a certain psychological state "toxic" one does not explain it. It is felt that the "toxicity" (in the traditional sense) has very little explanatory value for the observations made in the present study for the following reasons:

(a) The drug was reduced whenever the tolerance level was passed, i.e. whenever behaviorally there was evidence of organicity and toxicity; (b) The emerging clinical picture during the drug period was not the usual toxic psychotic state, i.e. a picture characterized mainly by confusion and hallucinatory experiences. The clinical picture had a certain consistency which is not seen in the usual toxic state, which appeared nonspecific; (c) Because the aim of the study is psychodynamic investigation, the term "toxic" and "toxic state" itself has to be brought into psychodynamic frame of reference comprehensibly and cannot be dismissed as self-explanatory.

2. Dynamic Hypothesis.

It is submitted that the psychoanalytic frame of reference possesses adequate conceptual tools for the purpose of rendering comprehensible psychopharmacological events. The part of this frame of reference which we feel may have explanatory validity is the economic principal of the mind and the concept of cathexis, or cathecting energies included in this principle. The reason for this is that these concepts are compatible with the concept of drives about the organic origin of which there is a general agreement. As we have pointed out elsewhere[1-3] epistemologically it is easier to envisage that a chemical substance affects the drives in their organic source, rather than other parts of the psychic apparatus, which are psychological constructs. By considering the concept of energetics of the mind and cathexis, it becomes comprehensible to state that a pharmacological substance, by influencing the sources of drives, alters the distribution of cathecting energies, or mental intensities in different parts of the psychic structure, i.e. ego and super-ego, and thus brings about psychodynamic changes.

Ostow[10] has postulated the changes in the available ego energies as an explanation for the effects of some of the newer phrenotropic drugs. It is difficult to pin-point the topography of energetic shifts. However, in the present study, the observation that the prevalent and the common emergent mood was that of depression, leads to the inference that changes in internalized control system (super-ego elements) may more likely be the hypothetical locality of change. Evidently such rigid separation cannot be made in matters pertaining to the mind, and the probability will be that both areas of ego and super-ego energetics have to be considered. Additional observations to be taken into account are the emergence of aggressive drives in several instances. If we take the important role of super-ego in depressive states, it can be said that under meprobamate in a majority of instances the super-ego became over-cathected, particularly in neurotics (in schizophrenics there were cases of elation indicating an under-cathexis of super-ego). This over-cathexis can be seen as an aggressive over-investment resulting

from a change in distribution of aggressive drives, explaining the appearance of depression. It can be stated that the release of aggressive drives resulted in schizophrenics in a break in defense of withdrawal, leading to either an aggressive rejection of superego (elation and hypomania) or an aggressive investment of it (depression) according to the particularities of each patient's psychic struceure impossible to determine at present.

In neurotic patients the upsurge of aggression led to a disorderly lifting of repression, resulting in a considerable anxiety, introversion of aggression and the appearance of depressive states.

The other problem to be considered is the favorable therapeutic result after meprobamate. We submit two explanations for this: (a) Regression - progression hypothesis, which we have entertained on other occasions.[11,12] To put it briefly, it states that an induced regression beyond the pathological fixation points, and subsequent gratification of those needs (the frustration of which had produced the fixation) may result in the abandonment of fixations and a progression. This explanation may have been operative in neurotic patients who regressed during and progressed after the drug period. (b) Transference effect. By this is meant the introjection of a good external object (the therapist) once the defenses were broken down and aggression had emerged. The patients, instead of being punished for their aggression, were attended to in a non-punishing way. This explanation may have been operative in schizophrenics.

It should be reiterated that the above hypothetical considerations are tentative, presented as speculations which may guide the future studies in this area, and which may have more problem raising than explanatory value. We submit that regardless of the validity of these hypotheses, to develop a comprehensive psychopharmacology with the view of utilizing the drugs to influence directly the psychotherapeutic process, it is necessary to transcend gross behavioral studies and explore the intimate happenings in the mind concomitant with drug administrations. Such studies can be undertaken only with a small number of patients, which may prevent statistical validation of the data, but, nevertheless, may provide information for future exploration of small and smaller areas of enquiry.

Summary

1. To determine the effect of meprobamate on psychodynamic states, this drug was administered in an average daily dose of 10 gm to 15 patients (five schizophrenics, two borderline states, one depressed and one manic, and six neurotics).

2. A methodology particularly devised for psychopharmacological studies involving psychodynamic structure is described, having for its objective the detection of change in four areas of organization of ego, drives, object-relations and mood.

3. The regime of drug administration consisted of four periods: no-drug (2 weeks)—meprobamate (4 weeks)—no-drug (2 weeks)—and follow-up. Patients were seen from 2 to 3 times weekly throughout the experiment with a particular technique of interviewing described in methodology.

4. Psychological tests (Wechsler, Rorschach, Figure Drawings) were performed before and at the end of the drug period. Statistical analyses of test items were performed.

5. The fundamental change appeared to be that of mood (depression in particular) in the background of a regression-progression movement; the former mainly in neurotics and the latter mainly in schizophrenics. Two hypotheses are forwarded to tentatively explain the observations: organic and dynamic. It is submitted that dynamic hypotheses, using the economic principle of the mind and the concept of cathecting energies, may render comprehensible the changes.

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Discussion

Dr. F. M. Berger:

Dr. Azima's basic point of reference is entirely different from mine and for that reason it is difficult for me to discuss it.

His basic assumptions are psychoanalytical whereas I am more materialistically oriented. He speaks about ego and super-ego as tools. This does not have too much meaning for me. I have been trained to assume that there must be some material substrate such as enzymes that in some way produce an ego and these enzymes have to be located somewhere. Anyhow I agree with Dr. Azima's statement which he made in the introduction of his paper, that it is very important to go deeper, not to limit one's self to behavioral aspects but to try to explain further the deeper functioning of the mind.

I will confine my remarks to those parts of his paper where he used objective measurements of the changes. There are two such parts, the behavioral observations he made and the psychological tests he has carried out.

I was amazed to hear that his patients were not sleeping. He used meprobamate in doses of about 10 or 12 grams a day for a month and this is more than ten times the usual daily dose of meprobamate as used by clinicians in every day use. It is truly amazing that the patients who received such enormous doses of this central nervous system depressant should not be completely knocked out.

I think it is interesting to consider for a second why that should be. I believe it shows something that has been previously shown pharmacologically, that meprobamate does not affect the reticular formation. The midbrain reticular formation is the seat of consciousness and it is the area that is specifically attacked by barbiturates and all central nervous depressants. I believe Dr. Azima has shown in experiments in humans that meprobamate does not block the reticular formation. In monkeys and cats apparently the reticular formation is also not blocked.

What does meprobamate do then? Perhaps I may mention briefly what I believe to be the possible mode of action. The rhinencephalic-limbic system deep in the brain consisting of the hippocampus and the amygdala, the septum pelucidum and the nuclei of the thalamus has been mentioned. If you introduce an electrode in this part of the brain nothing happens. They are almost dead areas. If you give meprobamate and record again nothing happens but you can stimulate these areas and if you do you get a striking picture. You get a marked after-discharge, and a short train of stimuli will set up a pattern which looks like convulsions; high potential discharge, which lasts for a minute or so. A small dose of meprobamate given to an animal prior to the stimulation will cut this out, will abolish or limit the duration of these after-discharges in the limbic system. That may well be one of the modes of action of meprobamate.

You will ask, what do the phenothiazines do? They too have a very striking effect on this system but the system interestingly enough is affected in the opposite way. Chlorpromazine sets up these high potential discharges in the limbic structures, showing again that chlorpromazine and meprobamate act differently, at least on the limbic system.

Other observations that Dr. Azima made that are of great interest are the psychological tests and in his paper you can note that he has carried out 8 different procedures and he tested each patient before meprobamate and after several days with these enormous doses. Much to my amazement I noticed in the tables that only two out of these eight tests were significantly affected, which shows, again much to my surprise, that meprobamate even in these enormous doses has a relatively slight influence on the cortex, on association, learning, performance and perhaps imagination.

I just would like to close with one question. Dr. Azima has investigated the effect of large doses of barbiturates, of reserpine and of meprobamate in patients suffering from various mental disorders. I think it would be of interest if he could tell us briefly the basic differences he observed in these patients who have received these large doses of the three different agents.

Dr. Azima:

From the research point of view we have to search for linking concepts between physiology and psychology and to me the concept of "Energetics of the Mind" is applicable. It is difficult for me to conceptualize that the drug affects the psychological ego but it is more comprehensible in terms of shift of intensity. That is why I have elaborated on this part of the topic.

The second point that Dr. Berger brought up is about the patient not being sleepy. I think there were at least two reasons. One was which I did not mention but it is mentioned in the paper, is that these large doses were reached within ten days so that it is obviously a habituation process.

The second important point is that there is a dynamic difference between the effect of the barbiturates and meprobamate, and that is the production of this state of depression. As you know, in the depressive and manic states, one of the main complaints is lack of sleep. They cannot go to sleep. They did not go to sleep.

As for the difference between reserpine and barbiturate and meprobamate, I have not studied this specifically in neurotic patients. I stuudied only schizophrenic patients and I really have not put my data together to try to evaluate the difference. As far as meprobamate and barbiturate are concerned, I pointed out the main difference.

Dr. Holt:

I would like to ask Dr. Azima in regard to the apparent high frequency of depressive reaction, whether in the treatment of other patients, not previously depressed at much smaller levels, perhaps one-tenth of the amount used in the present study, clinical signs of depression or psychological signs of depression were evident. Inasmuch as Dr. Azima is using about 8 to 10 times the average therapeutic dose it may be that he is getting a paradoxical opposite effect to what we encounter at the much smaller dosage levels. Certainly my own clinical experience would suggest that meprobamate rarely produces depression in the doses that I use and if others have had a similar experience in encountering depression I would be interested in hearing about it.

Dr. Azima: I do agree that small doses of meprobamate do not give depression. There is relief of anxiety. However, this has to be comparatively studied. You have to take the same patient with an anxiety state, and try both periods the double blind way, a small dose and a large dose.

It seems that the small doses of meprobamate have an effect on anxiety and that the large doses on a variation of anxiety which is guilt feeling. Why this is so, I don't know, but I agree that the small dose gives no depression.

Dr. Leo Alexander:

I would like to point out that the authors have certainly made an important contribution to the body of opinion, showing that the effect of drug varies considerably depending on the pre-existing state of the patient.

We used a much simpler framework in our drug studies, namely, the psychogalvanic and cerebral alerting response and found it dependent upon the pre-existing mental state. A marked difference in response may be obtained, for instance, with some psychological states.

The divergence of response in schizophrenics and depressives in the conditioned reflex experiment is very interesting. It seems the schizophrenic can be conditioned with greater ease and better differentiation, especially in the acute stage, than even the normal and then meprobamate cuts down this excessively sharp differentiation. However, in a depressive in which there is an equivalent phase, a paradoxical phase, meprobamate enhances it. So in a general sense meprobamate relieves inhibitions and Peterson has also shown it releases the inhibition of the inhibited bladder reflex. So the release of inhibition is an interesting feature of meprobamate.

We all are perhaps like the three blind men describing the elephant. We all look at different parts of the same picture but the exciting thing is to put all these parameters together and a total picture will ensue. That I believe is in the line of future development of psychiatry.

In medicine we speak of pneumonia, yet it is very important to follow adrenal function in pneumonia and so perhaps in spychiatry we are gradually learning to utilize varying parameters of the disease and getting more the whole point of view.

Dr. Azima: What Dr. Alexander has brought out is very interesting. What I did not elaborate on but which is in the paper, if there is a release of inhibition of drive, the schizophrenic cannot regress because he is already at the low level. So he has to progress. He can do this if there is a good external object there to help him. The neurotic patient has to regress. According to Pavlovian concepts, I think this progression or regression can come to a comprehensible frame of reference.

Dr. Anna Daniels: I would like to ask Dr. Azima how did this study end as far as the patients were concerned? Did you continue them forever under the high dosage? Did you diminsh the dosage gradually and what was the effect and how did you end your experiment with the patients?

Dr. Azima: The meprobamate was stopped at the fourth week. Meprobamate was used for 30 days and stopped.

Dr. Daniels: What happened to the patients?

Dr. Azima: Out of the 15 patients there were only three patients who relapsed. The rest have been discharged from the hospital and they are all right as far as I know with no other medication.

Dr. Karlin: Did you get any convulsions?

Dr. Azima: We had two.

Effect of Phenothiazine Derivatives on Liver Function

WOLFRAM KEUP, M.D.

The appearance of jaundice as a side effect of chlorpromazine (CPZ) medication was described soon[1-4] after the drug had been introduced into psychiatric therapy.[5] Deschamps[6] reported the death of a patient with delirium tremens and liver cirrhosis which seemed to be related to CPZ medication. These reports raised some questions:

1) Does CPZ have a toxic effect on the liver tissue?
2) What is the pathophysiological mechanism of CPZ jaundice?
3) Is the appearance of liver cell dysfunction and of jaundice dependent on the dose of the drug?
4) Does a history of liver damage predispose to CPZ jaundice?
5) Can CPZ damage further a liver with impaired function?
6) What is the prophylaxis and therapy of liver dysfunction by CPZ?

Much clinical and experimental work has been done to find answers to these questions but most of them have not been answered in a satisfactory manner. Since the advent of the newer phenothiazine derivatives the question has been raised whether they have the same side effects on the liver as CPZ. It has been unfortunate that this question has not been given sufficient attention in the choice of the newer drugs. Almost all investigations deal with CPZ. In 1954 we studied the liver function of psychiatric patients receiving CPZ[7] and recently we had the opportunity to study the effect of other phenothiazine derivatives upon the liver.[8] We shall attempt to answer the above mentioned questions from our own personal experiences and from a review of the literature.

Methods

In 60 psychiatric patients during therapy with different phenothiazine derivatives a battery of different serum protein tests was carried out which had previously proven useful in a large number of patients with internal medical diseases:[9,10] Colloidal red flocculation,[11] cephalin cholesterol flocculation,[12] thymol turbidity and flocculation test,[13] Weltmann's coagulation test as modified by Frimberger,[14] Takata reaction as modified by Mancke and Sommer,[15] sublimate turbidity time according to Frimmer,[16] formalin gelatinization test[17] and cadmium sulfate reaction as quantitatively modified by Keup[18] were done. In addition serum bilirubin determinations were made. In patients where liver dysfunction was suspected the galactose tolerance test as modified by Ludwig[19] was carried out if the psychiatric condition of the patient allowed it. Control studies were carried out for three days prior to the administration of the drugs. Liver function was tested weekly for up to 12 weeks. Patients with somatic diseases were excluded from the study. In addition to CPZ we investigated three experimental drugs of the phenothiazine group: KS 75, KS 33 and TP 21 (Mellaril; all Sandoz Ltd.). The chemical formulae are shown in fig. 1.

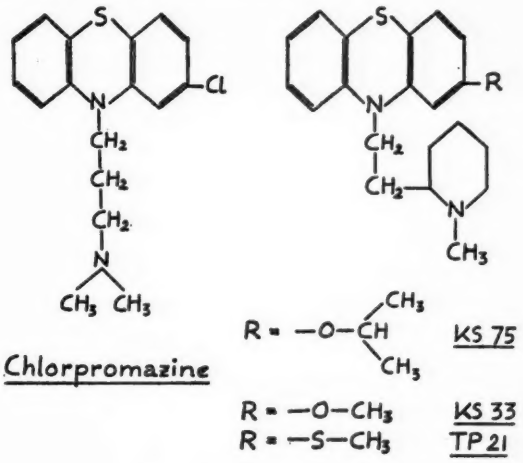

Fig. 1.

The daily drug dosage varied between 50 and 400 mg. CPZ was given intramuscularly during the first days of therapy. It was replaced by oral administration as soon as the psychological condition of the patient allowed it. The three other drugs were administered orally only.

In evaluating our method it must be noted that almost no "liver function test" to date is a specific test for liver damage. The serum protein reactions are very sensitive and must therefore be evaluated in a test bat-

From Research Facility, Brooklyn State Hospital, Brooklyn, N. Y.

tery in which unspecific positive results usually can be detected. Serum protein reactions are not liver function tests in a true sense; however they have advantage over tolerance tests which utilize unphysiological substances (e.g. bromsulphalein) in that they do not alter physiological conditions. There is no evidence that these tests are influenced by altered metabolic states. Serum protein reactions indicating liver dysfunction were found in 13% of somatically untreated schizophrenic patients; the meaning of these findings for the present study has previously been discussed.[7] Following the suggestion of Ask and Hagnell[20] we have utilized the galactose tolerance test as a control of the protein reactions. Galactose is a physiological substance and the specificity of the tolerance test is well known. Patients with galactorrhea during CPZ therapy[21] were excluded. The effect of CPZ on the carbohydrate metabolism and specifically on galactose tolerance remains to be studied.[22]

Results

During the course of therapy two different types of serum protein test reactions were observed: Those of the exudative-inflammatory type and of the liver parenchyma type.[9,10] The appearance of both types was not related in time but in some patients they overlapped. The reactions of the exudative-inflammatory type appeared during the time of parenteral medication and disappeared shortly afterwards, whereas the hepatocellular reaction type was independent of the method of administration. The galactose tolerance test in the second part of our study confirmed the validity of the liver cell reaction in serum proteins. We interpret the exudative-inflammatory changes as a result of tissue irritation by the drug injected, but we leave open the question whether this may not be partially the consequences of regulative processes.

Changes of the *exudative-inflammatory type* were seen in 75% of the patients in the beginning of CPZ administration. They were always slightly positive only and in duration exceeded the parenteral administration from one to two weeks. In patients receiving oral medication from the beginning we occasionally found a single positive serum protein test but they never tended toward the exudative-inflammatory reaction type. The same holds true for the oral administration with KS 75, KS 33 and TP 21. As a trial we replaced oral administration of KS 75 by intramuscular injection for five days during the course of therapy. This was followed by the prompt appearance of the exudative-inflammatory reaction type (values obtained three days after injection was started). These reactions disappeared six days after oral medication had been substituted.

Hepatocellular reactions were observed in 8 of 40 patients receiving CPZ who were tested weekly. This is 20% of the patients treated, with the reservation that this is not a statistical valid sample. Hepatocellular reactions were also found in two of six patients treated by KS 75 with another reaction being questionable. No hepatocellular changes were found in 10 patients treated with KS 33 and 4 patients treated with TP 21. The ndings are summarized:

TABLE 1

Hepatocellular Reactions of Serum Proteins During Treatment With Several Phenothiazine Derivatives.

	Weekly Controls		Single Controls			Total	
	No.	Liver cell dysfunction	No.	Liver cell dysfunction	Cholostatic reaction	No.	Liver cell dysfunction
Chlorpromazine	40	8	21	1	1	61	10
KS 75	6	2+(1)	8	–	1	14	3+(1)
KS 33	10	–	20	(1)	–	30	– (1)
TP 21	4	–	6	–	–	10	–

According to our experience this type of change in the serum proteins is related to liver cell dysfunction. With the exception of some rare cases of chronic tuberculosis, subacute bacterial endocarditis, ankylosing spondylitis and others[9,10] we saw the same type of reaction only in patients with clinical or subclinical liver disease. We did not see it under the influence of drugs acting on the autonomic nervous system.

The onset and course of the hepatocellular changes in patients treated with CPZ and KS 75 is shown in fig. 2.

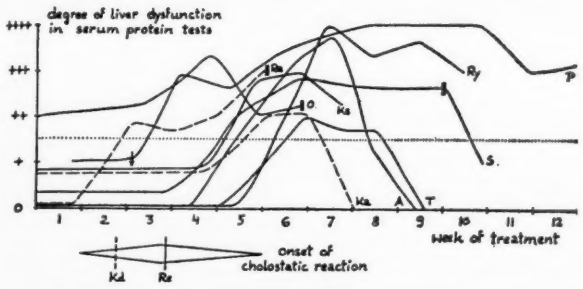

Fig. 2. Onset and course of hepatocellular changes in the serum protein reaction with chlorpromazine (———) and KS 75 (- - - - -) respectively. || = administration interrupted, ψ = asthmatic attack.

All reactions of the liver cell type occurred between the second and fifth week of treatment. In almost all of the 116 patients listed by Doughty[23] in his survey of CPZ jaundice, reported in the literature, the jaundice appeared in the second or third week of therapy, while in a few cases it occurred during the first, fourth or fifth week. This corresponds strikingly with our findings. As can be seen in Fgure 2 all grades of hepatocellular reaction were observed in our group of patients. The most severe signs were found in a patient (P, fig. 2) who had an asthmatic seizure before the onset of these changes. This patient had no previous history of asthma. It is interesting to note that allergic reactions directly followed by jaundice are reported in the literature.[24 25]

The course of the liver dysfunction in these patients was always benign. Alerting symptoms or clinical signs of liver disease were not observed. In some patients the pathological serum protein reaction disappeared although the medication was not discontinued. In one patient (S, fig. 2) with persisting pathological signs the reactions were normalized after discontinuance of the drug. In another patient in whom medication was continued only a slight improvement was seen during the tenth and eleventh week of therapy (P, fig. 2).

A *cholostatic reaction* was observed in two of our patients who were controlled weekly: A typical CPZ jaundice in a paranoid schizophrenic patient with a jaundice of unknown etiology in her anamnesis appeared on the twentieth day of therapy. Before the onset of jaundice and in the first four weeks thereafter (when the jaundice had already lessened) the serum protein tests remained normal, while in the fifth week after the onset of jaundice some of the serum protein tests and the galactose tolerance test became positive although CPZ had been discontinued with the onset of jaundice. A young catatonic patient who had 300 mg KS 75 per day became subclinically jaundiced on the twelfth day of treatment. The medication was discontinued but the serum bilirubin slowly went up to 2.4 mg% and still was elevated seven months later when we lost contact with this patient. Other causes of jaundice could not be detected. Serum protein reactions and galactose test remained normal.

We obtained the impression that the appearance of a reaction of the exudative-inflammatory type was a good sign as far as the psychiatric prognosis of the patient is concerned.[7] This may be explained by the experience that a patient who is not yet reduced to a pronounced "rigidity of adaptation"[26 27] in somatic *and* psychiatric reactions usually has a more hopeful psychiatric prognosis than a torpid patient. This impression was confirmed recently by Consbruch and Faust.[138] We furthermore feel that the appearance of the liver cell type of reactions is related to a bad psychiatric prognosis although we have no explanation for this.

Discussion

Doughty[46] in 1955 summarizing 116 cases of jaundice found an incidence of jaundice in 1.4% of hospitalized patients receiving CPZ. To date more than 300 cases of jaundice are reported in the literature.[1-4 7 24 25 28-97] The incidence of jaundice varied between 0.1%[65] and 5%[32] with an average of about 1%. Pollack[84] reports that he found in the first group of 500 patients an incidence of 4% and within the following 3300 patients an incidence of 0.35% only which he could not explain. Although most of the cases normalize within the first weeks, the duration of jaundice shows a large variation: A yellowish coloring of the sclerae for some hours only[30] and fully developed jaundice of a duration up to seven months resistant to any treatment[31] was observed. The disease is mostly benign but a number of fatal cases have been reported.[6 75 98 99-101] However, the relation to CPZ administration was not always obvious.

The clinical syndrome of this type of jaundice may be supposed as known; a thorough description was given by Werther and Korelitz.[93] The jaundice is of the intrahepatic obstructive type as it may be caused by other drugs: arsphenamine,[102 103] isonicotinic acid hydrazide,[104] sulfonamides, phenacemide, aureomycin and others.[65] According to Werner et al.[105] the obstructive jaundice caused by methyltestosterone is different from the arsphenamine type in some details.

Corresponding to different experimental and clinical data obtained in the past few years the question of whether phenothiazine derivatives can have a toxic effect on liver parenchyma was answered in a widely varying manner. We will report briefly first the negative results, then the results indicating the possibility of liver cell damage and its conditions.

Denying the possibility of a liver cell damage by CPZ the following experimental data were presented:

A daily dosage of two mg. CPZ per kg. in white rats was tolerated over long periods without any histological sign of liver damage.[106] "Practically no influence on the liver" was found by Courvoisier et al.[107] in different laboratory animals with even fatal doses of CPZ (see [108]). Wirth[109] treated rabbits and cats for months with high doses of CPZ without finding changes in liver tissue or choleresis. Scholz and Kretzschmar[110] confirmed that CPZ alone will not hurt the liver of the rat but they observed histologically that an intrahepatic cholostasis could be detected when CPZ was given together with some well known liver poisons.

Clinically:

Some authors deny the occurrence of liver cell function in nonicteric patients[21 29 45 198] treated by CPZ. Careful studies only should be reported here: The following tests were carried out every three or four days during a period up to two months in a group of 30 internal medical patients and in a second group of 33 psychiatric cases by the team of Kinross-Wright, Moyer and Finney:[64 65 81] Serum alkaline phosphatase, serum bilirubin, bromsulphalein test, thymol and cephalin-cholesterol reaction and the test for urobilinogen in the urine. No indication of liver damage was found. Cohen, Archer and Nash[39 40 195] controlled the liver function of 14 patients carefully and of another 70 patients less frequently by similar tests. They found some positive results in different tests and serum bilirubin was increased on three occasions but they did not conclude that a disturbed liver function could be the cause of these changes. The liver function of 8 patients receiving high doses (1500 to 3500 mg. per day) of CPZ was followed without evidence of liver damage.[113]

Some suicidal attempts by an overdose of CPZ have been reported.[114 115] These have offered the opportunity to investigate liver function under toxic conditions but unfortunately the results of liver function tests were not reported. However, the patient of Vallat and Lepetit[115] survived a dosage of 22.4 mg. CPZ per kg. after a coma of five hours without any evident clinical signs of liver injury. Samuels[116] observed a pathologically increased serum alkaline phosphatase level during the second to ninth day after a suicide attempt with 5-10 g. of CPZ. He relates this finding to liver damage.

The possibility of liver damage by CPZ was confirmed by the following experimental data:

Swelling of the liver cells, mainly in the center of the liver lobule, but no degenerative signs were found by Laumonier et al.[117] in rabbits receiving 25-100 mg. CPZ per kg. They also observed swelling of liver cells in their jaundiced patient. They believe that this sign is essential for a true hepatosis. Of the mice receiving (5-)10 mg. CPZ per day subcutaneously 10% died with massive liver necroses in the experiments of David.[118] Jaundice was not found. An increase of glycoproteins and glycogen, sometimes of the nucleoproteins, and a slowly increasing fatty degeneration of mostly intermediary localization was observed histologically. David relates the increase in the number of mitoses and in the size of nuclei with vacuolization to an increase in the activity of CPZ detoxication in the cells. The liver seems to have an important role in the detoxication of this drug;[109] with regard to this it is interesting to learn that patients with anamnestic liver

disease showed increased responsiveness to CPZ,[43 81 119] an effort known for other drugs too, e.g. LSD-25. The increase of liver glycogen in the experiments of David[118] was accompanied by hyperglycemia in the beginning of the drug administration only. Liver cell dysfunction as a cause of hyperglycemia in patients receiving CPZ has been discussed.[22] Irregular decrease of glycogen in some jaundiced patients was observed[113] in opposition to the experimental findings mentioned above. The influence of CPZ on the liver damaged by different liver cell poisons was studied by Popper et al.[120] They did not see an important influence of CPZ on the rat liver damaged by obstruction of the biliary tract, by chloroform, and by a diet rich in fat and poor in proteins. But worsening of the histological state and of esterase activity and serum alkaline phosphatase and at the same time an increase of serum bilirubin was observed under the influence of CPZ in rats with "single cell liver necrosis." We feel that this is an important finding as far as worsening by CPZ of pre-existing liver damage in patients is concerned. A peculiar granulation of the liver cytoplasm of the dog was observed after CPZ narcosis with the addition of small amounts of ether. These changes were not seen under the influence of ether alone.[128] The dog usually has high sensitivity for phenothiazine derivatives; a dose of two CPZ per kg. sometimes produces a slight urobilinuria.[106] Liver cell damage with vacuolization, but without fatty degeneration, was seen in dogs after intravenous application of larger amounts of CPZ as a regular result by Cima;[121] five mg. per kg. intravenously always were tolerated without any changes. Cima mentions that the same signs can be seen in acute hypoxemia. He therefore relates his findings to depression of oxygen uptake in the tissues under the administration of CPZ.

Clinically some signs of liver cell damage in nonicteric patients in relation to CPZ administration were observed too: The same histological changes found in patients with CPZ jaundice can be found in some of the non-jaundiced patients with the same complaints.[31 122] Usually liver cell tests are negative in these cases but in one of the patients of Azima and Ogle[31] pathological values were found in serum alkaline phosphatase, cholesterol esters and urobilinogen in the urine; serum protein tests were normal. Sims et al.[123] controlled 16 patients by liver biopsy during the course of CPZ therapy: They found in four of these patients cell infiltration in the periportal spaces, while in four others questionable states were seen. Among 47 nonicteric patients pathological values for the serum alkaline phosphatase were detected in 11, and other liver function tests as well as serum protein reactions were positive in an irregular way.[124] Fifty patients during CPZ therapy were controlled every second day by Dickes et al.[25] by means of bromsulphalein, serum alkaline phosphatase, serum bilirubin and cephalin-cholesterol tests. At some time during treatment 21 of these patients had signs of liver dysfunction in these tests; 13 of the patients showed improvement although medication was continued. In 8 therapy was discontinued because of the liver dysfunction. A pathologic bromsulphalein retention and an increased content of bile acids in the urine was found in three of 29 CPZ patients by Garmany et al.[126]; Dundee[127] reports that one patient out of 16 had signs of liver cell damage in serum cholinesterase and several serum protein tests; two other patients showed questionable results. Impairment of liver function as shown in the bromsulphalein test was seen by Flach[100] when CPZ was combined with ether in narcosis. This finding comes close to those seen by Stieve[128] in the dog.

Changes in serum protein content and protein lability during CPZ therapy were observed by different authors: Acceleration of the sedimentation rate,[129-131] a positive cephalin-cholesterol reaction in up to 50% of the patients,[24] decrease of albumin, an increase of beta-globulin[20 133] and gamma-globulin,[20] and positive protein flocculation tests.[20 132]

Regulation of Liver Cell Dysfunction?

The sedimentation rate is sensitive to influences of the autonomic nervous system. In vagotonia,[134] in case of "vegetative dystonia"[135] and in catatonia[136] sedimentation may become very slow. Its acceleration by a mainly sympatholytic substance like CPZ[129 130 131] would not be understandable without further details.

A decrease of albumin and a significant increase of alpha-globulin and sometimes of the beta- and gamma-fractions were seen by Schmidt et al.[137] following brain operations as well as other operations touching the brain only slightly. These changes were normalized 9 to 10 days after the intervention. They were considered as a "trophotropic regulation" caused by stress. Such a monotonous and highly unspecific reaction was described by Wuhrmann[136] as "one-sided inverse regulation mechanism between albumin and globulin."

Since a physical trauma is an equivalent in this regard to an operation, the same process was found in post-traumatic psychoses by Consbruch and Faust:[138] Decrease of albumin and increase mainly of the alpha$_2$-globulin fraction was followed by counter-regulatory tendencies between the sixth and twelfth day and normalization on the 28-30th day An operation is a trauma complicated by narcosis. Both, narcosis and trauma, represent a double action: Most of the usual narcotics influence the normal liver function.[100 128] The trauma requires the metabolization of cell debris and the synthesis of new proteins and charges the protein metabolism in this way; the response of the body is seen in the decrease of serum proteins and albumin mainly and in the negative nitrogen balance.[139] Both, narcosis and trauma, are at the same time a stress. According to Hartenbach and Ritter[140] a decrease of albumin, beta-, and less of the gamma-globulin together with an increase of the alpha-globulin is a common effect of adrenal hyperactivity by ACTH stress. The total serum protein decreases slightly at the same time. Such a regulation was previously[141] supposed on the basis of animal experiments. Lesions in the hypothalamic area cause hypalbuminemia and hyperglobulinemia in a monotonous manner.[142] It seems probable that the liver is the activated organ in this regulation controlling the composition of the serum protein.[143] An increase of albumin associated with a decrease of globulins can be produced according to Morimoto[144] by stimulation of the sympathetic centers in the brain but the same effect can be seen by stimulation of the hepatic plexus and by injection of epinephrine;[49] Kertal et al.[49] believe that this is the effect of mobilization of the blood deposited in the liver which may have a different protein composition. But here, as in the role of the sympathetic system with regard to the etiology of liver diseases,[145] insufficient data are available.

The influence of neuroplegic substances upon the regulation of the serum proteins has been studied by Schmidt and Matiar:[146] Changes appearing after brain operations were diminished and shortened by CPZ. The same changes in protein composition as seen in traumatized control cases were produced by CPZ, reserpin and tofranil (G-22355, Geigy) only when Consbruch and Faust[138] started medication immediately with high doses; otherwise only insignificant and slight changes were observed. Hippius et al.[147] believe that all changes in protein composition may be caused by regulative influences of CPZ, reserpin and mepazin (Pacatal), and that the conclusion that they may cause a liver dysfunction is not justified. We feel that already the earlier statement by Consbruch and Faust[138] mentioned above makes this belief doubtful. Since trauma and neuroplegic medication act in the same manner when observed separately[138] the reduction of the postoperative changes by tranquilizing drugs[146] cannot be caused by a counter-regulatory effect. The result of the regulation observed[138]—hypalbuminemia and alpha$_2$-hyperglobulinemia — probably could be misunderstood as an exudative-inflammatory type of serum protein composition but not as the liver cell type.

However, it is possible and even probable that a regulative component is included in our results as we mentioned previously,[7] but with regard to the type and the severity of the reactions and to the fact that they could be confirmed by the galactose tolerance test, we believe that the changes seen were liver-specific. We are less sure as far as the exudative-inflammatory type of reaction in relation to the parenteral administration of the drugs is concerned. But the coincidence in time[7 20 131 132] is obvious even when the drug is given in the middle of the treatment.

Summarizing, a certain role of the liver in the regulation of the serum proteins seems to be sure but it is not yet known what part liver anatomy and physiology contributes to

the regulatory processes and where regulation ends and disease begins. For this reason we use the term liver dysfunction instead of liver damage in our study.

Other Phenothiazine Derivatives

The unsubstituted phenothiazine itself has a toxic action: Among eight children receiving four g. of phenothiazine per day as an anthelmintic for several days Hubble[148] saw jaundice in two of them accompanied by anemia which was not severe enough to explain the jaundice as hemolytic in origin. The jaundice occurred within the clinical syndrome of a "hepatitis"; details are unfortunately not reported. Hubble mentions that liver toxicity and toxic action on hematopoesis is a common effect of substances containing benzene rings. Today phenothiazine is still used as an insecticide and in veterinary medicine and it is interesting to learn that photosensitization, as seen with some of our phenothiazine derivatives, is caused in young cattle followed by keratitis.[149]

Promazine (Sparine, Prazine) seems to be less liver cell toxic in experimental animals than CPZ.[150] Jaundice caused by this drug has been described infrequently;[151] no final conclusions are possible as to its effect on liver cell function at the moment.[152 153]

As far as the relation between *chemical structure and liver cell toxicity* is concerned Cima and Porro[150] conclude that the phenothiazine nucleus substituted with Cl in position 2 must be responsible for the liver toxic action. If that is true and if the side-chain does not influence this toxicity we would expect that prochlorperazine (Compazine, Stémétil), perphenazine (Trilafon) and 2-chloro-promethazine (Smith, Kline and French Lab.) must have the same liver toxicity as CPZ. But no reports are available concerning this question. It seems to us to be too early to establish a relation between chemical structure and liver toxicity. KS 75 which seemed to have an influence on liver function in our experiments is different from CPZ in substitution in position 2 as well as in the side-chain (see fig. 1).

It seems to us too premature again to draw any conclusions concerning liver toxicity from the *metabolic action* of the phenothiazine derivatives. CPZ is reported to depress oxygen uptake by several tissues[154] and to uncouple phosphorylation.[155-158] The concentration of CPZ in the liver is relatively low.[159] The conclusion of Cima[121] that a diminished oxygen uptake followed by a general depression of liver metabolism may cause liver dysfunction is only theoretical.

Is jaundice accompanied by liver damage?

In CPZ jaundice serum bilirubin, serum cholesterol,[148] and serum alkaline phosphatase[124] are reported to be increased. The serum alkaline phosphatase seems to be very sensitive and to rise earlier than serum bilirubin[160] in some cases but sometimes it remains completely normal.[82] A low serum prothrombin was found[54] which responded well to vitamin K medication[75] indicating a normal liver cell function.[161] All these tests are typical for the obstructive type of jaundice rather than for the liver cell type.[162] An increase of serum glutamic oxalacetic transaminase generally considered as a sign of liver cell injury was also found in CPZ jaundice[63] but the interpretation is not clear.

Histologically, biliary stasis, biliary thrombosis, cell infiltration in the periportal areas,[4 81 94 113] and sometimes pericapillary edema[124] is seen in CPZ jaundice. Usually the liver cells were found to be normal[54 163] and only in some cases swelling of liver cells,[70 117 164] fatty degeneration,[94] mostly as focal degeneration together with atrophy and pyknosis without total necrosis,[73] but in other cases focal necrosis also[48] was observed. The fatal case reported by Boardman[98] showed central necrosis and lobular atrophy but was complicated by rheumatic heart disease. Progression to fibrosis was observed.[61 82]

The *function* of the liver cell at the onset of the cholostatic hepatosis was usually found normal[4 89 93 113 165] even when hepatocellular degeneration was observed[73 94] or the jaundice persisted over a long period of time.[31 71 72 82 94] But on the other hand, it is not rare that pathological liver function tests,[36 166] especially bromsulphalein retention,[63] sometimes lasting longer than the hyperbilirubinemia,[72] were observed, indicating liver cell damage. The galactose tolerance test may be negative even when liver cell injury can be discovered histologically[73] or may become positive as in our patient with

CPZ jaundice.[7] Decrease of cholesterol esterification was observed in closely related methyltestosterone jaundice.[105] Dougty[23] summarizes his report with the words "that there is no evidence to indicate that the parenchymal tissue of the liver is more than transiently affected." We would like to add: Usually not more than transiently, but sometimes severe consequences can be seen.

The pathophysiological mechanism of CPZ jaundice is not yet explained satisfactorily. The following theories are discussed:

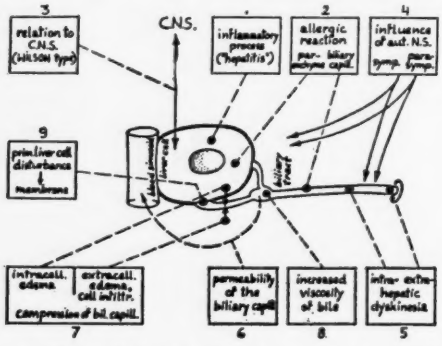

Fig. 3. The etiologic theories of chlorpromazine jaundice.

1) In the first publications the term "CPZ hepatitis" often was used,[51 55 56 77] but later on it became clear that *inflammatory* signs are missing at least in the beginning of the disease.[165]

2) An *allergic* etiology was supported by the observation of other allergic symptoms during CPZ therapy:[84] urticaria and maculopapular rash in patients[1 24 30 31] and nurses handling the drug,[167] drug fever,[126] asthma[24] and eosinophilia.[1 55] Eosinophilic infiltration in the liver was observed.[93] The allergic etiology is furthermore confirmed by the regularity with which jaundice appears within the second to third week after the onset of treatment,[1 23 31 65 72] by the fact that jaundice can appear exceptionally up to 16 days after discontinuance of medication,[25 41 57 66 74] and by the observation that its occurrence seems to be independent of the dose administered; jaundice was reported following the uptake of 25+10+10 mg. CPZ,[97] of 50 mg.[25] and 3x50 mg.[168]

The strongest counter-argument to the allergic etiology is the fact that patients can be treated by CPZ without relapse, after the jaundice has passed.[39 45 53 84 126 169] Shay and Siplet[124] tried to explain this on the basis of sensitization. Recidivation was observed in a few patients only.[1 84] The recognition of CPZ jaundice as an allergic disease does not allow us to state whether the biliary capillaries[48] or the liver cells[61] are affected.

Idiosyncrasy as an etiological factor was discussed too.[65]

3) Since parkinsonism occurs as another side effect of CPZ therapy a correlation between *central nervous system* symptoms and liver dysfunction of the type of Wilson's disease was supposed.[32 133] Some other indications for a possible relaxation between the central nervous system and liver dysfunction may be seen in the observation of acute disturbance three weeks after CPZ therapy was started[64] and in a patient with bulbar paralysis who became jaundiced 10 days after recovery from his neurological symptoms.[46] These results are not sufficient proof for this concept at the present time.

4) Influence of the *autonomic nervous system* was supposed.[43 117] The authors based their concept on the experimentally induced hepatitis of sympathetic origin investigated by Brocard[145] and on the speculations of Mosinger[170] concerning liver damage caused by central affection. "Emotional jaundice" seems to be caused by central autonomic dysregulation.[171 172] The adrenals may be involved in this,[173] but no proof has been given.

5) The dependence of the *mobility of the biliary tract* not only on the autonomic nervous system but also on the intramural nerve elements and mechanical influences opens the way for further speculation. Menguy et al.[174] found that an increase of the relative tonus of the biliary sphincter coupled with a relaxation of the biliary ducts results in a decreased internal pressure in the biliary tract when dogs received 10 mg. CPZ per kg. intravenously. After cholecystectomy on the other hand the internal pressure increases after CPZ medication.[175] A relation seems to exist with decreased mobility of the duodenum produced by CPZ.[47 174] From these results extrahepatic obstruction has been postulated as a possible cause of CPZ jaundice.[54] The predominance of female patients with CPZ jaundice[58 95] recalls the predominance of women among patients with biliary calculi. Besson[176 177] believes that the dyskinesia of

the smaller biliary vessels produces an intrahepatic obstruction.

6) An *increased permeability of the biliary capillaries* caused by some toxic damage mainly of the ampullar part on the periphery of the lobule with consequent permeation of bile into the blood was thought to be the first step in hepatocellular jaundice by Ohno[178] (1930). Watson and Hoffbauer[179] later supposed the same mechanism to be responsible for the onset of cholangiolitic hepatitis. According to Shay and Siplet[124] such a mechanism would explain the increase of serum alkaline phosphatase in CPZ jaundice before the serum bilirubin starts to rise since the phosphatase seems to be produced in the epithelium of the biliary canaliculi.

7) A *compression of the biliary capillaries* followed by stasis and jaundice may be produced by cell infiltration of the liver[123] or by a pericapillar edema.[124] Disturbance in the blood flow in the predamaged liver was seen by Trutschel[180] as a consequence of CPZ medication which may cause local edema. Bersohn and Wallace[164] suppose that swelling of the liver cell as an allergic reaction may produce compression of the biliary capillaries. Here the primary process appears to be in the liver cell itself.[70 117] But neither cell infiltration nor edema and swelling can be found in all cases of CPZ jaundice.

8) An *increased viscosity of bile* followed by stasis is supposed to be the cause of methyltestosterone[105] and CPZ jaundice.[75 90] The increased viscosity should be the consequence of primary liver cell disturbance.[75]

9) A *primary liver cell disturbance* was already presumed by the two last mentioned theories as the final cause of CPZ jaundice. Kalk[61] supposes that the cholostatic hepatosis begins as a toxic liver cell disturbance without any inflammatory signs on the membrane between liver cell and biliary capillary and that a hypersensitivity of the cell for CPZ may be involved. He cites the experiments of Hanzon[181] and Kulpe.[182] These authors were able to observe in rats and cold-blooded animals by means of the in vivo fluorescein method that the toxic liver cell damage begins on the membrane liver cells biliary capillary with vacuolization, probably as a kind of inner excretion within the cell, and then slowly progresses backwards into the cytoplasm followed by necrobiosis of the entire cell. These changes start mainly in the center of the lobule[182] in which a more intensive secretion of bile was observed.[181] Under influence of CPZ first signs can be seen in the center too. The described functional disturbances can be observed before any morphological change is detectable by common histological methods. We feel that this does not adequately explain the stasis within the biliary capillaries but it may be that a liver cell injured in this way produces a bile with increased viscosity or a tendency towards coagulation. Here we may recall the experimental production of a cholostatic reaction when CPZ was combined with a liver cell poison.[110]

In the *prophylaxis of CPZ jaundice* various investigators attempted to support the normal function of the liver cell, by the addition of carbohydrates in form of sweet tea,[183] cholic acid in combination with hexamethylentetramin (Felamin),[184 185 186] vitamins[187] and other agents.[188] The occasional pronounced success of these protective measures seems to us practical proof for the theory of a primary liver cell injury.

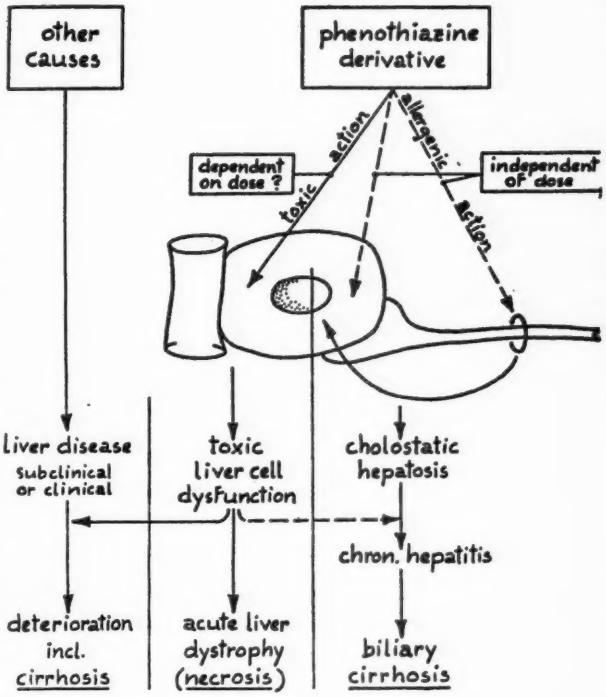

Fig. 4. Possible unfavorable consequences of liver cell dysfunction by chlorpromazine and chlorpromazine jaundice.

The *therapy of CPZ jaundice* with choleretic and liver cell protective drugs has had practically no success. ACTH and cortisone seem to be the only drugs which may shorten the duration of jaundice.[43 48 74 90 95] Patterson et al.[189] pointed out that cortisone not only has a choleretic but also a hydrocholeretic action so that its effect in the conditions of increased viscosity of the bile could be understood.

The *possible unfavorable consequences* of the supposed liver toxicity and jaundice caused by CPZ are summarized briefly:

A) *Cholostatic hepatosis—chronic hepatitis —biliary cirrhosis.*

In jaundiced patients Shay and Siplet[124] found some signs of a disturbed fat metabolism which can be interpreted as forerunner of a cirrhosis. We mentioned already that liver cell degeneration with atrophy and pyknosis[73] and fibrosis[51 82] were observed in some of the patients. Kelsey et al.[62] saw in 3 of 20 bioptically controlled patients with CPZ jaundice the transition to chronic hepatitis with persistent positive liver function tests. Kalk[61] followed in one patient the stepwise change from simple CPZ jaundice to chronic intermittent hepatitis and finally to a biliary cirrhosis, in this special case axanthomatous cirrhosis. Whitfield's[94] patient probably represents such a case too.

B) *Toxic injury—acute yellow liver atrophy.*

Elliot et al.[99] saw a patient whose CPZ dose raised within one week to 1600 mg. per day. Three days later a toxic erythema was observed. The patient died over night with the signs of acute aseptic liver necrosis. Another case with acute yellow liver dystrophy was seen by Kalk.[190] An acutely disturbed patient of Stenbäck[191] died in a shock after having fallen into an irreversible hypotonic state 21 hours after his last CPZ dose (100 mg. per day i.m.) On autopsy degeneration of the liver and kidney parenchyma, petechiae and edema of the lungs were found. The relation to CPZ medication remained questionable in this case.

C) *Worsening of existing liver disease?*

Most of the patients with chronic liver diseases had no signs of progressive liver dysfunction when treated by CPZ.[54 64 119 192] In a large series no essential worsening of alcoholic liver damage was observed.[193] But some authors advise caution in patients with liver damage.[46 65 72 121] The degree of the pre-existing liver damage seems to be important, particularly if it is just on the borderline of decompensation. The fatal case of Deschamps[6] had delirium tremens together with liver cirrhosis, that of Boardman[98] seemed to have liver congestion in consequence of heart disease. According to the experiments of Popper et al.[120] one would believe that the kind of pre-existing liver damage may also be of importance.

In 22 carefully studied patients with *CPZ jaundice* no anamnestic liver disease was found by Werther and Korelitz;[93] our patient had an anamnestic jaundice. But generally the incidence of jaundice seems not to be higher in patients with anamnestic liver damage than in others[81 125 193] and it may only be an unusual coincidence that just one of the first patients with CPZ jaundice studied by liver biopsy had signs of a subclinical liver involvement.[3] But experimental intrahepatic cholostasis appeared only when CPZ and a liver poison were given together. Here again the kind of liver damage was important: Liver necroses by allyl alcohol were even slowed down by CPZ.[110]

Comment

From the findings reported above we conclude that a certain liver toxicity of some phenothiazine derivatives can not be denied especially where high doses have been given experimental animals. The clinical consequences should not be underestimated but the 1% incidence of CPZ jaundice in the patients and its estimated mortality of 4%[127] demands caution and prophylaxis! The term "potential liver toxicity" as used by Kinross-Wright and Moyer[65] in describing the action of CPZ on the liver seems to us to be appropriate. Unfortunately our knowledge is still insufficient as far as the special conditions are concerned in which the potential toxicity becomes manifest. It seems to us that liver function can be affected in two different ways: 1) A toxic effect acts directly on the liver cell, causing slight liver cell dysfunction. This dysfunction may become the basis of rare complications, it does not seem

to represent a disposition to drug induced jaundice. 2) An allergenic effect of the drug acting on the liver cell and/or on the biliary capillaries causes jaundice but causes no or only late liver cell dysfunction. This dysfunction may be the first step towards the complication of jaundice. Since both mechanisms can be found or are absent in some of the phenothiazine derivatives a close relationship between them is assumed but at the moment no explanation can be offered without becoming speculative.

Finally the initial questions will be answered:

1) CPZ is doubtlessly a potential liver poison. However it seems that other auxiliary, hitherto unknown causes, are necessary to evoke manifest clinical liver symptoms.

2) The pathophysiological mechanism of CPZ jaundice is not yet definitley known. The most probable explanation is the following: A primary subclinical toxic liver cell damage combined with an allergic reaction of the liver cell produces disturbances on the membrane liver cell/biliary capillary with consequent excretion of an abnormal bile into the biliary capillary leading to stasis and intrahepatic obstruction.

3) The incidence of CPZ jaundice seems not to be dependent on the dosage. Nevertheless, the liver cell dysfunction produced seems to be favored by quickly increased and very high doses of the drug. We feel that increasing the daily CPZ dose over 1000 mg. rarely gives better psychiatric results. If the therapeutic result of such a dosage is not sufficient one should change to another drug instead of risking the still insufficiently known toxic actions.

4) A preexisting liver cell damage seems not to dispose to CPZ jaundice.

5) A serious anamnestic liver damage may be aggravated by CPZ. In case of light preexisting liver injury CPZ therapy may be tried if it is possible to control the liver function after the fifth week of treatment.

6) Prophylaxis of CPZ jaundice by liver cell protective substances is effective and therefore indicated. Therapy of jaundice still is problematic; some effects may be seen with cortisone.

In this study we stressed chiefly the possibility of impaired liver function by several phenothiazine derivatives conscious of the fact that this latent danger may only affect a very small percentage of our patients. We did this because we feel that this effect was astonishingly neglected when new phenothiazine derivatives were selected. We would always prefer a new derivative out of this group to CPZ if it has about the same psychological action without incurring the danger of obstructive jaundice and liver cell dysfunction with possibility of complications.

Summary

In 60 psychiatric patients with weekly controls and another 55 patients less carefully studied during therapy with different phenothiazine derivatives (chlorpromazine; KS 75-, KS 33-, TP 21-Sandoz) transient and slight liver cell dysfunction was observed in about 1/5 of the patients receiving chlorpromazine and KS 75. In addition in both of these drugs the cholostatic reaction was observed. A possible relation of the two mechanisms of liver dysfunction is discussed and the literature is reviewed. More consideration should be given to the potential liver toxicity of phenothiazine derivatives when new derivatives are used in therapy.

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Histopathologic Findings in the Liver and C. N. S. Following Administration of Tranquilizing Drugs

L. ROIZIN, M.D., G. EROS, M.D., G. GOLD, M.D., F. WEINBERG, M.D., W. H. ENGLISH, M.D., and T. WODRASKA, M.D.

During recent years, pharmacological research has developed a large number of drugs with neurotropic properties. The available information thus far indicates that: (1) some of these drugs are effective in certain mental disorders: (2) knowledge of their specific action on nervous tissue is fragmentary and scanty; (3) these drugs appear to be not only neurotropic but also possess some general and viscerotropic character; (4) variable species and individual susceptibility; (5) due to a combination of factors 3 and 4, side effects have been observed following the use of some of these drugs, even within the range of therapeutic dosage.

Up to the present time, much of the information concerning the action of tranquilizing drugs has been obtained from clinical observations, and neurophysiologic, pharmacologic, and biochemical investigations. Very little information about structural modifications resulting from these drugs is available in the literature, and it appears that some of the toxic effects would indicate actual structural involvement.

The above facts have prompted us to undertake correlated histologic, histochemical, and electron microscopic investigations of the central nervous system and viscera of human and experimental animals. In cooperation with Doctors True and Knight, we have previously presented at the meeting of the A.R.N.D. some preliminary clinicopathologic observations dealing principally with acute and chronic experimental investigations in laboratory animals, following the administration of chlorpromazine.

The present report concerns primarily with the review of the literature and some of the most outstanding hepatic and central nervous system histopathologic aspects in four biopsies and ten post mortem cases.

Adverse Effects of Chlorpromazine and Reserpine

To adequately evaluate the possible structural findings in the studied cases, we feel that it is necessary to present a general and, of necessity, short review of the reported adverse effects of these tranquilizing drugs in humans and animals and to then focus our attention on the more serious side effects which may represent actual structural alterations.

Because of the numerous and diversified reports appearing in the literature and in order to simplify the final correlation of this mass of clinical material with the subject of our discussion, we have summarized the available data in the following categories:

Cardiovascular, endocrinologic and neurohumoral, secretory, acute toxic, dermatologic, renal, articular, gastrointestinal hematologic and central nervous tissue effects.

The present review will be limited only to hepatic and neurological complications.

Jaundice and Liver Dysfunction:

Up to the present time a total of 322 cases have been reviewed from the literature, and 10 of our own cases.

All of these cases were treated with chlorpromazine with the exception of one case which had combined chlorpromazine and reserpine. Among these cases 38 biopsies of the liver were made. The histopathologic findings are discussed separately.

Neurological Complications:

To date we have reviewed a total of 1,653 cases from the literature which we feel is

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The author, for this paper, was awarded, jointly with others, the R. Thornton Wilson annual award for his contribution to psychiatric research and treatment.

only a sample of the probable number of their total occurrence. Of these, 1429 had parkinsonian or parkinsonian-like symptoms, 76 disclosed dystonic-like symptoms, 136 presented epileptiform seizures, and 12 others showed miscellaneous involvement of the central and peripheral nervous system. We did not calculate the average age of the patient at the time of the occurrence of neurological complications because many authors did not include this information. However, where age has been reported, it appears that parkinsonism was noticed as early as 24 years and as late as in the senile period. Of the 1,429 cases, sex was reported in only 246, 203 women and 43 men. Only a few investigators mentioned whether their cases were drawn from a total hospital population or from separate female or male services. For the other two major varieties of neurological complications, the clinical reports are so incomplete that figures for age and sex would have no significance except that in the epileptiform group, the sex of the patient was mentioned in 63 cases, and in each instance it was female. Of the 1,653 patients developing neurological complications 928 were on chlorpromazine, 288 on reserpine, and 437 on combined reserpine-chlorpromazine therapy.

Comments

Jaundice and Liver Dysfunctions:

The study of 322 cases collected from the literature and our own 10 cases indicates that jaundice and liver dysfunction were more frequently observed in females. That they occurred predominantly with chlorpromazine treatment. That their duration varied from 4-130 days, and that they developed at varying dosages—25 mgs. to 1,600 mgms. per day. In the vast majority of cases the jaundice and liver dysfunction were confirmed by laboratory tests and/or liver biopsies. In both instances it appears that they were related predominantly to a biliary stasis and in those cases in which biopsy of the liver was done the architecture of the liver was well preserved except in a few instances in which moderate lipid degeneration was noted. In the large majority of the cases the jaundice and liver dysfunction appears to be transitory and reversible in character (4-240 days). In a few cases it lasted for a longer period of time when associated with pre-existing liver pathology or when death occurred. In the latter instance the most common alterations appear to be due to an obstructive type of biliary stasis similar in character to those observed in some experimental investigations. In our cases as well as those reported in the literature the biliary stasis was sometimes associated with biliary thrombi in the central canaliculi and deposits of biliary pigment in the hepatic parenchymal cells and Kuppfer cells. In some few instances this pigment was noted in the epithelium of the kidney tubles and bile casts were observed in the lumina of the renal tubules. At times fatty degeneration of the hapatic cells of the central zone and/or periportal and peribiliary fibrosis (one case) were also encountered.

All these findings indicate: (1) The observed liver dysfunctions have a low percentage of incidence; are mild, transitory and reversible in character, and thus might indicate some possible idiosyncracy. (2) The severity of the dysfunctions and pathologic findings appear frequently related to preexisting abnormalities of the hepatobiliary tract or the co-existence of the other disease processes which might have an effect on the liver (i.e., chronic alcoholism), gastro-enteric disorders, etc.

Neurologic Disorders:

In reviewing the 1,653 cases with neurologic complications, those with parkinsonian, parkinsoniform or pseudo-parkinsonian-like symptoms constituted the largest group (1,429 cases). Next in frequency were epileptiform seizures (136 cases), followed by dystonic-like symptoms (56 cases). The remainder of the neurologic complications were represented by a heterogeneous group consisting of delirium tremens-like (5 cases), cerebellar-like (1 case), and tabes-like (1 case) symptoms. In one case paroxysmal spasms of the larynx, tongue, and neck were observed.

Of the total number of cases, 928 were on chlorpromazine, 288 on reserpine, and 437 on combined reserpine-chlorpromazine treatment. It appeared that the adverse

neurologic complications are independent of dosage (25-7,500 mg. of chlorpromazine; 3-15 of reserpine and on combined treatment 300-700 mg. of chlorpromazine and 3-5 mg. of reserpine) or duration of treatment (1-365 days). In some alcoholics seizures appeared on the first day of treatment. Otherwise there was no obvious time relationship between the duration of treatment and the appearance of neurologic signs.

As in the cases with liver dysfunction and/or agranulocytosis, these complications were generally transitory and reversible. However, in a few cases, secondary complications led to death.

Autopsy and Neuropathologic Findings:

Of the total of the 29 reported deaths in the literature, 19 were autopsied and in only three of these was direct mention made of central nervous system findings. The neuropathologic findings in the first case were reported as cerebral congestion, acute swelling of the neurones of the hypothalamus and thalamus, and scattered petechial hemorrhages. In the second case there were no significant findings except for convolutional atrophy of the frontal lobes, and aneurysm of the left carotid artery and brain edema. The last case was partially reported in a symposium on chlorpromazine. No mention was made of the sex or age of the patient. However, it is reported that the brain showed changes in the subthalamic body, globus pallidus, and scattered changes in the hypothalamus.

In our ten studied cases, the most significant histopathologic findings consisted of various degrees of chromatolytic changes in the nerve cells of various areas of the brain cortex, basal ganglia, thalamus, hypothalamus, and cerebellum. In addition a questionable degree of chromatolysis was noted in the mesencephalon pons and medulla. In one case, the severe neuronal changes noted could also be related to co-existing Huntington's chorea.

It is interesting to note that in three cases neuronal disorganization was pronounced in the hypothalamic nuclei and in three cases the Purkinje cells and the neurons of the dentate nuclei were decreased in number as well as undergoing, in various degrees, lipid degeneration. Also increased perineuronal sattelitosis and various stages of neuronophagia was observed in four cases.

It would be difficult and indeed hazardous to attempt a correlative evaluation of the neuropathologic findings and tranquilizing drugs based on the three cases reported in the literature and our own 10 cases. This is because that: (a) as a group they represent too small a number upon which to base such an evaluation; (b) the observed alterations were not specific in character, and (c) in all of them death was due to complicating factors (agranulocytosis with secondary infections, jaundice or liver dysfunction, post laporatomy complications, E.C.T., aging factors, etc.). These factors could have caused or increased the severity of the observed structural alterations. However, in view of the frequency of extra-pyramidal and diencephalic symptoms (thermo-regulatory disorders, diabetes insipidus, neurohormonal and neurovegative disorders, etc., it would appear that the studied tranquilizing drugs may have some predilection for the basal ganglia, the neurovegative centers in the hypothalamic region and mesencephalon.

Conclusions

On the basis of the review of the literature as well as on the basis of our own material it appears that:

(1) The liver dysfunctions are frequently associated with structural changes caused by biliary stasis of an obstructive variety. The clinical and pathologic findings are generally mild, transitory and reversible in character, thus indicating a possible relationship to idiosyncracy or constitutional predisposition. The severity of the dysfunction and the pathologic findings appear frequently to be related to pre-existing abnormalities of the hepato-biliary tract or to the existence of other disease processes which might have an effect on the liver.

(2) The adverse neurological reactions are represented predominantly by extrapyramidal symptoms followed in order of decreasing frequency by epileptiform seizures and dystonic-like symptoms. The frequency and intensity of epileptiform attacks appears to be related also to predisposing factors (questionable history of previous epilepti-

form manifestations, post-lobotomy, and associated with E.C.T. treatment).

(3) Definite conclusions concerning characteristic structural alterations as the basis for the observed neurological complications cannot be drawn from the neuropathologically studied cases reported in the literature (3 cases) or from our own personally studied 10 cases because their number is too small when compared to the number of discussed complications and because these cases appear to be associated with other pathological processes which could have conceivably masked or intensified whatever changes were present. However, the structural alterations of the basal ganglia, some hypothalamic and mesencephalic structures observed in some of the human cases may possibly be the result of a neurotropic activity of the studied tranquilizing drugs.

(4) The liver dysfunction, agranulocytosis, and neurological complications appear in general not to be related to dosage, duration of treatment or age. Generally they were mild, transitory and reversible in character. In the majority of cases clinical recovery followed upon decrease or interruption of drug therapy.

(5) The increased severity of the above discussed complications, in certain predisposed individuals strongly militates against indiscriminate use of these drugs.

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For bibliography, the reader is referred to:

L. Roizin, Chas. True, and M. Knight: Structural Effects of Tranquilizers. *Proc. Assoc. Res. N. M. D.*, 37:285-324, 1959.

Prognostic Application of Psychological Techniques in Convulsive Therapy

ROBERT L. KAHN, PH.D., and MAX POLLACK, PH.D.

One of the more important clinical applications of psychological testing techniques is the prediction of the results in psychiatric treatment. In particular, there has been a considerable effort to determine valid psychological prognostic criteria for the somatic therapies. The results to date, however, have not found clinical acceptance.

Using the Rorschach, for example, Rabin[1] has stated that "single Rorschach factors cannot serve as indices or as predictors of improvement." In contrast Piotrowski has published a number of papers on the prognostic use of the Rorschach in insulin coma and convulsive therapy.[2-6] Unfortunately, his criteria, as reported in successive papers, are vague and contradictory. In 1941 he reported six explicit prognostic signs which were applied in predicting clinical response over a period of several months after the termination of treatment. But Rees and Jones,[7] in a study of schizophrenic patients receiving a variety of somatic therapies, found that Piotrowski's signs were related to the results on a chance basis only.

The differences in the studies of various investigators can be accounted for by methodological variables. These variables include factors of population, number of patients observed, the method of analyzing data, the kind of somatic therapy utilized, and the criteria for evaluating improvement, including the time at which the clinical evaluation is made in relation to the course of treatment. Another basis for inconsistent results may be the lack of an adequate theoretical framework.

For the past several years we have been engaged in studies of the convulsive therapy process. These studies were initiated to test a hypothesis concerning the mode of action of convulsive therapy which was derived from observations on a brain-damaged population. According to the hypothesis of Weinstein and Kahn[8,9] the therapeutic effect of convulsive therapy was related to the induction of altered brain function creating the necessary conditions for a new type of symbolic adaptation, mainly denial, in characterologically disposed persons. Our previous studies have already shown that altered brain function is a necessary condition for behavioral change[10,11] and that the manifestation of denial language patterns with treatment is related to the evaluation of improvement.[12] The purpose of the present report is 1) to summarize the findings on personality factors and 2) to demonstrate the application of these findings as prognostic criteria for convulsive therapy.

Method

These studies were conducted at Hillside Hospital, a non-profit, voluntary, mental hospital, admitting patients who are considered as having early and curable illnesses. Psychotherapy is the principal treatment employed, with somatic therapies available when needed. The material presented was collected in a series of studies during a period of three and a half years. While a total of 180 patients have been investigated, varying numbers were tested with each of the techniques of personality evaluation. The patients ranged in age from 20 to 66, with a median of 45, and included twice as many women as men.

All patients received convulsive therapy administered three times a week, using either a Medcraft alternating current instrument or a Reiter C-47 electrostimulator. A minimum of 12 treatments was given, with the total course determined by the supervising psychiatrist in charge of the convulsive therapy unit. All psychological procedures were administered in the week prior to the start of treatment.

The determination of the patient's response to treatment was based on the medi-

From the Department of Experimental Psychiatry, Hillside Hospital, Glen Oaks, N. Y.

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cal director's evaluation at the time of discharge, usually within six to eight weeks following treatment.

Procedures and Results

1. *Family Interviews.* According to the original theory, it was considered that persons showing characteristics of the "explicit verbal denial" personality, as described by Weinstein and Kahn[13] would be most likely to show a behavior change rated as improvement following treatment. This was tested in a standardized interview with members of the patient's family, eliciting information on the patient's attitudes, mode of communication and reactions to stress. Fifteen areas of behavior considered to be related to denial tendencies were scored from the interview material. A score of 0, 1 or 2 was given for each item, depending on whether the designated behavior was minimally, moderately or markedly shown. The sum of the scores thus obtained was used as the denial score.

The relatives of 47 patients were interviewed, and denial personality scores ranged from 0 to 25, with a median of 11. The patients were divided into two groups: those with scores from 11 to 25 were classed as "high denial," and those from 0 to 10 as the "low denial" group.

The results of this analysis were significant, showing that of the patients with high denial scores, 58% were in the much improved group and only one patient was unimproved. Of the patients with low denial scores, on the other hand, only 30% were much improved and an equal number were unimproved.[14]

Although these results based on family interviews were promising, we felt that our conceptions of prognostic personality factors could be extended and made more amenable to practical application by the use of standardized psychological procedures. For this purpose the Rorschach test was used.

2. *The Rorschach Test:* We have obtained Rorschach protocols in 87 patients receiving convulsive therapy. The records were scored according to the criteria of Klopfer and Kelley.[15] Only those components were analyzed which were considered related to the personality aspects under study.

It was found[16] that the much improved patients had significantly fewer total number of responses, and a significantly greater percentage of whole and form responses than did those patients who were rated as unimproved. The stereotypy and limited imaginative capacity of the much improved patients was also shown by their giving a greater percentage of popular responses, with little diversification of content categories. They were less likely to have any kind of shading response. Those patients who had human movement (M) responses had the poorest clinical responses, while those with no movement of any kind had the best results. With respect to color, an FC response was associated with a poor clinical result, while those with no color at all did very well.

Combining some of these factors tended to sharpen the differentiation in terms of outcome. Thus, of those who had both M and FC, only 17% were rated as much improved. In contrast, of those with neither M nor FC, 66% were much improved and only one patient was unimproved.

We have converted these results into prognostic criteria, as shown in Table I. In one column are listed those Rorschach factors which have been most closely related to a favorable prognosis. In the other column are those factors which are prognostic of an unfavorable clinical outcome. For example, of those patients with ten or less responses 67% were much improved. Only 28%, however, of those with 16 or more responses had a good result.

It should also be noted that comparison of posttreatment Rorschach records with those obtained prior to treatment failed to show any significant change. This confirms similar observations by others[6,17-19] and indicates that the Rorschach pattern is probably a reflection of the basic personality rather than transient aspects of the disease process.

3. *Social Attitudes: The F Scale.* While these Rorschach results amply confirm the concept of the relation of personality factors and results of treatment, further data was obtained in application of measures of social attitude such as the California F Scale. This scale, originally developed in studies of eth-

TABLE I

	Favorable Prognosis		*Unfavorable Prognosis*	
		% Much Improved		% Much Improved
Number of Responses	10 or less	(67%)	16 or more	(28%)
Movement	None	(63%)	M present	(28%)
Color	No FC	(60%)	FC present	(21%)
F %	75 - 100	(59%)	0 - 59	(27%)
Shading	None	(58%)	Present	(33%)
M and FC	Neither Present	(66%)	Both Present	(17%)

nocentrism and authoritarianism[20] has been increasingly used in the study of more central psychological processes. In our laboratory the F Scale has been regarded primarily as a reflection of stereotyped thinking and communication. It has been observed that patients who receive convulsive therapy at Hillside Hospital have significantly higher F scores than those given psychotherapy alone.[21]

In these studies a ten-item modification of the F scale[22] has been used. The test is rapidly administered, taking no longer than 10 minutes in most cases. The subject reads 10 ambiguous statements and indicates whether he agrees or disagrees with each statement, and to what extent. The score given for each item ranges from one to seven and the range of total scores is 10 to 70. The greater the agreement, the higher the score obtained. The statements themselves are extreme, convntional or stereotyped expressions. For example, one of the statements is: "If people would talk less and work more, everybody would be better off."

This test has been given to 96 patients prior to convulsive therapy. Using a score of 40 as a cut-off point, we found that of those patients with scores of 40 or more 71% were rated as recovered or much improved. In contrast, only 36% of those with scores below 40 were so rated. In general, the higher the score, the better the clinical result.

We have also tested an additional 13 patients, referred for convulsive therapy, but who either refused treatment or terminated it of their own accord prior to completion. Of these, eleven had F scores below 40, an observation consistent with the general expectation that such persons have a poor response to convulsive therapy.

Discussion

These observations have shown that in the course of the investigation of theoretical problems of convulsive therapy, certain standard psychological procedures have provided data which is significantly related to the therapeutic outcome. This data can now be applied to the practical problem of clinical prognosis.

We have found that a favorable improvement rating is given to those patients who develop euphoric, hypomanic or denial modes of adaptation following treatment.[23] Such behavioral change is most likely to occur in persons whose premorbid personalities may be characterized as non-empathic, non-introspective, non-verbally communicative and highly conventional and stereotyped with little imaginative or creative capacity.[14] On the Rorschach prior to treatment these patients give few responses, fail to show human movement, shading or integrated color responses (FC), and have little variety of content. On the F Scale, their scores were apt to be over 40, showing a high degree of stereotypy in their communication.

In contrast to such patients, others are either unchanged by convulsive therapy or develop such modes of reaction as panic, paranoid behavior, or increased somatic concern, such as complaints about their memory. These patients are rated as unimproved. While this latter group of patients showed diverse patterns in their premorbid personality characteristics, they were more apt to be imaginative, introspective and less stereotyped in their communications. On the Ror-

schach they gave human movement, integrated color and shading responses, and were more diversified in their content than the good prognosis patients. On the F Scale their scores were most likely to be under 40.

The finding that meaningful prognostic criteria can be derived on the basis of personality constellation rather than in terms of nosological entities has important implications. For one thing, this conception leads to the use of further psychological techniques for prognostic purposes. Such application is currently under way in our laboratory at Hillside Hospital. Secondly, it is possible to derive an increased understanding of mental disorders, their management and prevention. Thus, we have previously noted[14] that the same personality factors which are related to a good prognosis with convulsive therapy, are etiologically important in the development of certain types of psychiatric disorder. Studies of patients with psychotic depression, for example, demonstrated a prominence of premorbid personality patterns characterized by the inability to communicate verbally,[24] and rigidity and lack of imagination.[25] Such persons are generally refractory to conventional verbal techniques and require non-verbal therapeutic techniques. It seems that the same personality factors which make a person responsive to non-verbal forms of therapy are involved in his susceptibility to a depressive reaction. The same stereotypy and conventionality which lead to a catastrophic response in the individual faced by the sudden loss of a job or close relative, permit the development of denial, minimization and displacement under the conditions of altered brain function and are considered "improved" by the family and the therapist.

Summary and Conclusion

We have shown that in the course of investigation of theoretical problems of convulsive therapy, certain standard psychological procedures have provided data which is significantly related to the therapeutic outcome. This data can now be applied to the practical problem of clinical prognosis.

On the Rorschach test, those patients without human movement, shading or integrated color (FC) responses, with few total responses, and with little originality or variety of content have the best prognosis. On the F Scale, a score of less than 40 is prognostic of a poor clinical response.

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Discussion

Dr. Paul H. Wilcox: I would like to ask if there is any record of a psychiatric procedure which does change the Rorschach pattern in an individual.

Dr. Kahn: On the basis of my own experiences and the literature, by and large the Rorschach pattern is pretty stable. There are relatively few procedures that you can induce and get a marked change in the patient. You sometimes do see changes in persons who have severe degrees of brain damage and then as that has improved you may get significant changes. Even there you get a fairly constant record.

Dr. Leon D. Hankoff: Dr. Kahn, I was wondering how you define denial. The factor that discriminated between the improved and unimproved was the denial of mental illness, denial of symptoms or denial of any unpleasantness.

Dr. Kahn: The original studies on denial were based on brain tumor population. The denial was in terms of who denied the fact they were ill, had an operation, were in the hospital, etc. Then we were interested in this in terms of characterological properties and formulated a number of characteristics which we identified with people who showed this type of denial. They tended to be people who had a lot of drive, were conventional and stereotyped and kept their feelings to themselves. We formulated the concept of explicit denial type of personality. That was the theoretical concept when we originally studied these patients.

Dr. Carl Breitner: At the Hillside Hospital you use a Medcraft and also a Reiter machine. Have you been able to differentiate between the two since they have a different effect?

Dr. Kahn: We have not differentiated between the clinical effects of the two machines. We have done a convulsive and sub-convulsive control study, where we were unaware which patient was getting what treatment and we found significant differences between the people receiving convulsive therapy against those who received sub-convulsive therapy.

Dr. Leo Alexander:

During the war we tested the Rorschach responses in combat flying personnel in all accidents, and I published these observations in the Psychopathological Association meetings in 1950. The title was "Relation of the Psychological Test to Psychiatry." We found an interesting phenomenon. It may have some bearing on what the authors found. We observed that if an aviator was under stress and we repeated the Rorschachs, for instance during a combat tour of 35 missions, there was a gradual impoverishment of the Rorschach, increasing rigidity, less and less responses as if these people were battening down the hatches, limiting themselves you might say to the minimum of concrete responses.

On the other hand, if the aviator blew up with numerous responses, reflecting external stress, we called that threatening responses. Everything was bombs, splattered blood, splattered all over, responses which in peacetime we see only in schizophrenics. It is very interesting. We saw some Rorschach tests in combat aviators which in a peacetime setting, without knowing the history, we would call schizophrenic blood and gore. This was because the people were exposed to blood and gore. For example we noted the man who saw the head of his co-pilot shot off. Frozen to his knee he could see the head all the time while he was bringing in a disabled plane. In that particular stress situation we saw changes in the Rorcchach in that the experience is restricted. We saw men as outpatients who had the beginning of this response. The people who developed blood and gore had a bad prognosis but responded well to deep slee ptherapy with Sodium Amytal for three days.

I wonder if you would comment on the cutting down of responses. It is an interesting thing that normals have.

Dr. Peterson: I would like to ask Dr. Kahn if he feels there is a correlation between the poor shock response and the more schizoid type of personality, or sociopathic type of personality.

Dr. Kahn: Well, I suppose you can describe this in many ways, depending upon the point of view and the kinds of language patterns and so on. To a certain extent I suppose you could draw that kind of conclusion from the data. People who have a lot of movement responses and original responses and are rich in color are more apt to be called schizophrenic.

Rosters of Members

Eastern Psychiatric Association, Inc.

Alamprese, D. J.
1226 13th Avenue
Altoona, Pa.

Alexander, Leo
433 Marlborough Street
Boston 15, Mass.

Alexander, Saunders P.
44 Little Tor Road
New City, N. Y.

Anchel, David
105 Oxford Road
Rockville Centre, N. Y.

Anderson, Charles L.
120 North Oak Street
Hinsdale, Ill.

Arnot, Robert E.
51 Abbott Road
Wellesley Hills 81, Mass.

Ayd, Frank J., Jr.
6231 York Road
Baltimore 12, Md.

Ayres, Conrad M.
3205 Grand Concourse
New York 68, N. Y.

Azima, Hassan
1025 Pine Avenue N.
Montreal 2, Canada

Berg, Seymour
129 East 80th Street
New York 21, N. Y.

Berger, Frank
Wallace Laboratories
New Brunswick, N. Y.

Bergman, Jerome W.
255 Western Promenade
Portland, Maine

Berman, Harold H.
Willowbrook State School
Staten Island 14, N. Y.

Berson, Harold
909 President Street
Brooklyn 15, N. Y.

Bircher, Richard
Sandoz Pharmaceuticals
Route 10, Hanover, N. J.

Bolton, Leonard J.
108 Evergreen Avenue
Elmira, N. Y.

Breitner, Carl
Arizona State Hospital
Phoenix, Arizona

Brick, Harry
1817 Monument Avenue
Richmond 10, Va.

Brody, Matthew
41 Eastern Parkway
Brooklyn 38, N. Y.

Buckman, Charles
Kings Park State Hospital
Kings Park, N. Y.

Burdine, Winston Everett
160 Little John Trail NE
Atlanta, Ga.

Campden-Main, Brian C.
824 S. Arlington Mill Drive
Arlington, Virginia

Cancenllieri, Reno
1395 Pelham Parkway N.
New York 67, N. Y.

Carey, Thomas C.
111 Gillett Street
Hartford, Conn.

Carone, Pasquale A.
86 Voorhis Avenue
Rockville Centre, N. Y.

Carra, Angelo D.
43 Narcissus Drive
Syosset, L. I., N. Y.

Carrier, Russell H.
Carrier Sanitarium
Belle Meade, N. J.

Cassino, Frank A.
119-36 80th Road
Kew Gardens, N. Y.

Cerulli, Remo
133 East 58th Street
New York 21, N. Y.

Clare, Jack E.
465 West End Avenue
New York 28, N. Y.

Climo, Henry J.
55 Osner Drive N.E.
Atlanta, Ga.

Cohen, M. M.
10 West 74th Street
New York 23, N. Y.

Colvin, William
Burroughs Wellcome & Co.
Tuckahoe, N. Y.

Davis, William A.
Wallace Laboratories
New Brunswick, N. J.

de Beer, Edwin J.
264 Scarsdale Road
Tuckahoe 7, N. Y.

Denber, Herman C. B.
1750 Grand Concourse
New York 57, N. Y.

di Cori, F. A.
40 Fifth Avenue
New York 11, N. Y.

D'Isernia, Richard
16 North Broadway
White Plains, N. Y.

Dodds, Harold H.
604 Plant Street
Utica, N. Y.

Doltolo, Joseph
115 E. 61st Street
New York 21, N. Y.

Dorfman, Wilfred
1921 Newkirk Avenue
Brooklyn 26, N. Y.

Dunlop, Edwin
9 School Street
Attleboro, Mass.

Eliasberg, W. G.
151 Central Park West
New York 23, N. Y.

Elpern, Sidney
1749 Grand Concourse
New York 53, N. Y.

Epstein, Joseph
975 Park Avenue
New York 28, N. Y.

Eyres, Alfred E.
567 Fisher Bldg.
Detroit 2, Mich.

Falsey, Edward F.
237 77th Street
Brooklyn 9, N. Y.

Fenichel, Maurice
Kings Park St. Hospital
Kings Park, N. Y.

Fink, Max
11 Wensley Drive
Great Neck, N. Y.

Fischer, Abraham B.
4101-12 Avenue
Brooklyn 19, N. Y.

Folmer, Edward J.
15 East 36th Street
New York, N. Y.

Friedman, Emerick
497 State Street
Albany, N. Y.

Friedman, Jacob H.
1749 Grand Concourse
New York 53, N. Y.

Furst, William
50 So. Munn Avenue
East Orange, N. J.

Gabriel, Anthony R.
108 East 81st Street
New York 28, N. Y.

Gagliardi, Francis
177-30 Wexford Terrace
Jamaica, N. Y.

Gahagan, Lawrence H.
133 S. Lasky Drive
Beverly Hills, Calif.

Gallinek, Alfred
1165 Fifth Avenue
New York 29, N. Y.

Gibson, Augustus
Meck & Co.
Rahway, N. J.

Gilbert, Michael M.
316 N.E. 14th Terrace
Miami 32, Florida

Goldman, Douglas
179 E. McMillan Street
Cincinnati 19, Ohio

Goldman, Max
176 Bay State Road
Boston 15, Mass.

Goldstein, Louis
599 West 190th Street
New York 40, N. Y.

Gordon, Hirsch L.
239 Central Park W.
New York 24, N. Y.

Gralnick, Alexander
High Point Hospital
Port Chester, N. Y.

Greenhall, Armand L.
123 West 86th Street
New York 24, N. Y.

Gruenthal, Max
25 West 81st Street
New York 24, N. Y.

Hand, Morton
1620 Ditmas Avenue
Brooklyn 26, N. Y.

Handin, Irving L.
129 Country Club Drive
Elmira, N. Y.

Harty, John E.
101 N. Main Street
Waterbury 54, Conn.

Hochstetter, Werner
11 E. 68th Street
New York 21, N. Y.

Hoffman, Carl J.
2901 Cottman Avenue
Philadelphia 49, Pa.

Holt, William L., Jr.
Albany Hospital
Albany, N. Y.

Houck, Knut H.
579 Cottonwood Street
Acaville, Calif.

Hubbard, R. C.
109 Deer Hill Avenue
Danbury, Conn.

Impastato, David J.
40 Fifth Avenue
New York 11, N. Y.

Ivey, Evelyn P.
24 Elm Street
Morristown, N. J.

Kalinowsky, Lothar B.
115 East 82nd Street
New York 28, N. Y.

Kallmann, Franz J.
924 West End Avenue
New York 25, N. Y.

Karlan, S. C.
39-15 Main Street
Flushing, N. Y.

Kaye, Jesse J.
395 Quail Street
Albany 8, N. Y.

Kelly, F. W.
1351 Mt. Hope Avenue
Rochester 20, N. Y.

Kelly, John L.
138 Livingston Avenue
New Brunswick, N. J.

Kippen, Arnold A.
1121 Cleveland Avenue NW
Canton 3, Ohio

Lando, Santino
706 Madison Avenue
Albany, N. Y.

Lang, H. Beckett
644 A. Madison Avenue
Albany 8, N. Y.

Lesse, Stanley
239 Central Park W.
New York 24, N. Y.

Leuzzi, Anthony P.
30 So. Broadway
Yonkers 2, N. Y.

Lipton, Harry R.
490 Peachtree Street N.E.
Atlanta 8, Ga.

Lipton, Louis M.
1200 Fifth Avenue
New York 21, N. Y.

Locascio, Nicholas
133 East 58th Street
New York 22, N. Y.

Loscalzo, Anthony E.
124 East 40th Street
New York, N. Y.

Lotesta, Pasquale
812 Ocean Parkway
Brooklyn 30, N. Y.

Luwisch, Joachim
257 Lexington Avenue
New York 16, N. Y.

Malamud, William
The National Assoc. for
Mental Health, Inc.
10 Columbus Circle
New York 19, N. Y.

Mascort, Juan A.
706 Arlington Apts.
San Juan, Puerto Rico

McCartney, James L.
223 Stewart Avenue
Garden City, N. Y.

McGraw, Robert
2 East 85th Street
New York 28, N. Y.

Mearin, Robert J.
9 Lafayette Avenue
Brooklyn 17, N. Y.

Merrill, George G.
100 E. Chase Street
Baltimore 2, Md.

Merwarth, Harold R.
30 Eighth Avenue
Brooklyn 17, N. Y.

Miller, Jacob J.
1749 Grand Concourse
New York 53, N. Y.

Negrin, Juan, Jr.
108 East 81st Street
New York 28, N. Y.

Osinski, Walter A.
25 Upper Loudon Road
Loudonville, N. Y.

Osserman, Hyman
975 Park Avenue
New York 21, N. Y.

Pacella, Bernard L.
115 East 61st Street
New York 21, N. Y.

Padula, Louis J.
2790 Arlington Avenue
New York 63, N. Y.

Page, James A.
522 Midland Avenue
Berwyn, Pa.

Patry, Frederick L.
1917 14th Street W
Bradenton, Fla.

Pelzman, Oscar
107 No. Ocean Avenue
Patchogue, N. Y.

Pritcher, Leon
88820 Wilshire Boulevard
Beverly Hills, Calif.

Pujals, Ramirez Carlos
J. A. Saco 609
Santiago, Cuba

Rappa, James
681 Clarkson Avenue
Brooklyn 3, N. Y.

Reback, Samuel
16 East 84th Street
New York, N. Y.

Reiss, Max
Willowbrook State School
Staten Island 14, N. Y.

Reiter, Reuben
187 Sylvan Avenue
Leonia, N. J.

Revitch, Eugene
828 Madison Avenue
Plainfield, N. J.

Reznikoff, Leon
42 Robinson Terrace
Clifton, N. J.

Risquez, Fernando
Ota. Cubilets Av. Sucre
Caracas, Venezuela

Robie, Thedore R.
676 Park Avenue
East Orange, N. J.

Rosenbaum, Salo
50 East 72nd Street
New York 21, N. Y.

Ross, Ira S.
179 Irvington Avenue
So. Orange, N. J.

Rozett, Oscar
19 Prospect Street
Summit, N. J.

Rudoy, Martin U.
139-02 Grand Central Pkwy.
Kew Gardens, N. Y.

Rupp, Charles
133 So. 36th Street
Philadelphia 4, Pa.

Ryan, Gerard V.
Elmcrest Manor
Portland, Conn.

Ryberg, Percy E.
30 Fifth Avenue
New York 11, N. Y.

Sainz, Anthony
Marcy State Hospital
Marcy, N. Y.

Scharf, John H.
555 Park Avenue
New York 21, N. Y.

Simecek, Victor H.
87-27 169th Street
Jamaica 32, N. Y.

Shultz, Gertrude M.
Lakemont, Yates Co.
New York

Squilla, Vincent D.
1132 Allerton Avenue
New York, N. Y.

Stein, Calvert
71 Meadowbrook Road
Longmeadow 6, Mass.

Stern, Morton M.
24 Girard Place
Newark 8, N. J.

Sternbach, Abraham A.
2070 Grand Concourse
New York 57, N. Y.

Szafir, Paul
177 Nigh Street
Perth Amboy, N. J.

Telefeian, Alphonse
690 Congress Street
Portland, Maine

Terhune, William B.
Valley Road
New Canaan, Conn.

Thomason, Carroll S.
44 Madison Avenue
Morristown, N. J.

Tritt, Herman
365 West 263rd Street
New York 71, N. Y.

Victoroff, Victor M.
2231 Taylor Road
Cleveland 6, Ohio

Wender, Louis
59 East 79th Street
New York 28, N. Y.

Wilcox, Paul H.
526 West 10th Street
Traverse City, Mich.

Wilson, Gerald E.
Ontario Hospital
Kingston, Ont., Canada

Yanof, Zale A.
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